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STUDIES OF TERRAMYCIN, IN VIVO AND IN VITRO

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Received for publication April 18, 1950

Finlay and his associates recently reported the isolation of an antibiotic agent from broth cultures of a new species of soil streptomyces, *Streptomyces rimosus* (1). They named the agent "terramycin." According to these authors, terramycin is an amphoteric substance forming crystalline hydrochloride and sodium salts; it does not deteriorate during long standing at room temperature at a pH under 5; it is active *in vitro* against staphylococci, *B. subtilis* and a number of gram negative bacilli, inhibiting most strains at concentrations of 1 to 3 μg/ml. The strain of *Pseudomonas* that they tested required 100 μg/ml for inhibition and the strain of *Proteus* grew in the presence of 1000 μg/ml. They found the LD_{50} for mice, of terramycin administered intravenously, to be equivalent to 192 mg of the active (amphoteric) compound per kilogram of body weight. Finally, they reported that terramycin was effective in the control of infections induced in mice with haemolytic streptococci, pneumococci, *Klebsiella pneumoniae*, *Salmonella typhosa* and "other organisms".

Samples of the hydrochloride and sodium salts of terramycin were received at this laboratory in January 1950, through the courtesy of Dr. Gladys L. Hobby of Chas. Pfizer and Co. The hydrochloride has been submitted to the usual laboratory examinations carried out here in the case of new agents (2) and the results are embodied in this report. The sodium salt was compared with the hydrochloride in a few *in vitro* tests. As there was no difference in the behaviour of the two, the sodium salt was not tested *in vivo*.

METHODS

Agents. Two samples of terramycin hydrochloride were used; the first, lot OM 15, was put up in capsules containing approximately 270 mg each of greenish yellow powder. This was used during the first two weeks of testing. Then loose material, lot 450-25-B, was received. This was labeled as containing 905 μg/mg;

it presented the same appearance as the contents of the capsules. Both lots proved difficult to dissolve, requiring the addition of hydrochloric acid for the preparation of 0.5 per cent solutions. The amount of acid required was determined to be approximately 1 ml of N HCl to 10 ml of 1 per cent terramycin suspension. Solutions prepared in this manner were diluted with water to 20 ml, giving a final concentration of 5 mg/ml terramycin in N/20 HCl. The solution is bright yellow and has a pH of approximately 2. One to ten broth dilutions remain clear but tend to darken on standing, apparently through oxidation. The sodium salt of terramycin is an extremely light, fluffy substance of a dirty yellow colour. It is readily soluble in water at 10 mg/ml. At this concentration the solution is burnt-orange coloured and has a pH of about 9.

Aureomycin HCl, lot 7-8411, received through the kindness of the Lederle Laboratories was used as a standard of comparison in all of the tests.

In vitro tests. The minimal inhibitory concentrations of terramycin and aureomycin for representative strains of a number of bacterial species were determined by the serial dilution method, under the conditions described previously (2). The stability of terramycin, its filtrability through Seitz filters, the effect of changes in the size of the inoculum and of the presence of serum in the tests were determined by noting differences in the amount of drug required for inhibition under the various circumstances.

Therapeutic tests. The value of terramycin as a therapeutic agent was tested in mice experimentally infected with the strains of haemolytic streptococcus, pneumococcus, *Klebsiella pneumoniae* and *Haemophilus influenzae* employed in the work with neomycin and furadroxyl (3). The strain of *H. influenzae* had increased in virulence, during the winter, to such an extent that it was found necessary to reduce the number of organisms used in the infecting dose. Otherwise the method of producting the infections, and of treating them, remained the same.

RESULTS

In vitro tests. The minimal inhibitory concentrations of terramycin and aureomycin for bacteria of a dozen different genera are shown in Table I. In most instances terramycin inhibited growth at a lower concentration than aureomycin but the difference was not great, except in the case of strains of *Pseudomonas*. The inoculum used in these tests (in which the volume of drug-dilution was 0.5 ml) was 0.5 ml of a 1:10,000 broth dilution of the culture. However, changes in the size of the inoculum had but little effect on the end points of terramycin for *E. coli* and a strain of haemolytic streptococcus. About twice as much antibiotic was required for an inoculum of 0.1 ml of straight culture as for the usual inoculum, and half as much for an inoculum of 10^{-7} ml.

TABLE I

TABLE I

Minimal Inhibitory Concentrations of Terramycin HCL and Aureomycin
(20-hour readings)

ORGANISM	TERRA	AUREO	ORGANISM	TERRA	AUREO
	μg/ml			μg/ml	
E. coli 4	1.25	5	Streptococcus Group A C203	.156	.312
			Streptococcus Group A NY5	.078	.078
Aerobacter 7	1.25	5	Streptococcus Group A Cott	.039	.078
Aerobacter 8	2.5	5			
Aerobacter 10	.62	2.5	Streptococcus Group B 090	.156	.625
Aerobacter 12	.62	2.5	Streptococcus Group B 19	.156	.625
K. pneumoniae A	.62	1.25	Streptococcus Group C K61	.156	.312
K. pneumoniae B	1.25	5			
			Streptococcus Group D Zym	.312	.625
S. typhosa Fox	1.25	.62	Streptococcus Group D Bard	.312	1.25
			Streptococcus Group D H69D11	.156	.312
Proteus vulgaris 11	10	100			
Proteus vulgaris 17	100	100	Streptococcus faecalis Black	.312	.625
Proteus mirabilis 18	>100	100	Streptococcus faecalis Tarr	.312	.625
Ps. aeruginosa Call	6.25	50	Streptococcus viridans Will	.312	.312
Ps. aeruginosa Beid	6.25	100	Streptococcus viridans Keel	.312	.625
Ps. aeruginosa Aisq	3.12	50	Streptococcus viridans Dop	.625	.625
Ps. aeruginosa Wall	3.12	50			
			D. pneumoniae type I SV1	.156	.312
H. influenzae B 641	2.5	2.5			
			Staphylococcus aureus Zorn	.312	.625
Clostridium welchii BBL	.5	.1	Staphylococcus aureus Barl	.156	.312
Clostridium welchii HWD 11	.5	.1			
Clostridium welchii HWD 12	.5	.1	Staphylococcus albus Heat	.156	.312
Clostridium septicum BBL	.05	.01			
Clostridium sporogenes BBL	.5	.05	"Diphtheroid" Green	.156	.156
Clostridium novyi BBL	.05	.5			
Clostridium novyi HWD 8	.05	.1	B. subtilis Lederle	<.078	.078
Clostridium tetani BBL	.5	.1	B. subtilis FDA	.156	.312
Clostridium tetani HWD 7	.5	.1			

The inhibitory concentrations in Table I are those noted after 20 hours incubation. End points of both agents increased on further incubation. Those for aureomycin were 4 to 8 times higher and those for terramycin 2 to 4 times higher at 44 hours than at 20 hours. Aureomycin deteriorates rapidly at temperatures above freezing, especially in the presence of alkali. Finlay and his associates (1) found that terramycin hydrochloride lost no activity when held for long periods at room temperature at pH 2 to 5. In the present study, as shown by the data in Table II, it was found that terramycin did not deteriorate during 24 hours at room temperature at pH 5, 7.2 or 8.7. About 50 per cent of activity was lost after 24 hours at 37 C, but the loss was no greater in the neutral and alkaline environments than in the acid

TABLE II

The Effect of pH and Temperature on the Activity of Terramycin HCL

TEMPERATURE CENTIGRADE	DURATION OF EXPOSURE	pH 5.0	pH 7.2	pH 8.7
		Assay—μg/ml		
−20°	23 hr.	5	5	5
27°	23 hr.	5	5	5
37°	23 hr.	2.5	2.5	2.5
56°	2 hr.	2.5	2.5	2.5
100°	10 min.	0.31	0.62	1.25

Test organism: *E. coli* 4.

medium. Two hours at 56 C also resulted in a 50 per cent loss of activity, again regardless of pH. The pH of the environment, however, did have an effect upon the reaction of terramycin to 10 minutes exposure to a temperature of 100 C, and this in a direction opposite to that expected. There was a fourfold loss of activity when the heating was done at pH 8.7, and eightfold loss at pH 7.2 and a sixteenfold loss at pH 5.

Five ml of a 50 μg/ml broth solution of terramycin HCl were filtered through a small Seitz filter pad, in a Swinny adapter, with no loss of activity.

Effect of multiplication of E. coli. The effect of terramycin on bacterial multiplication was determined by plating out cultures containing various concentrations of the hydrochloride at intervals after they

had been inoculated with the standard strain of *E. coli*. The results are presented graphically in Figure 1. A slow decline in population occurred with even the smallest amount of drug—the equivalent of 1 minimal inhibitory concentration. The duration of the period of decline increased with the amount of drug present, but with concentrations up to 10 μg/ml growth appeared sooner or later. With 20 μg/ml, although there were 510 organisms per ml at 72 hours, there were only 10 at 96 hours and no turbidity developed during the 10 day period of observation.

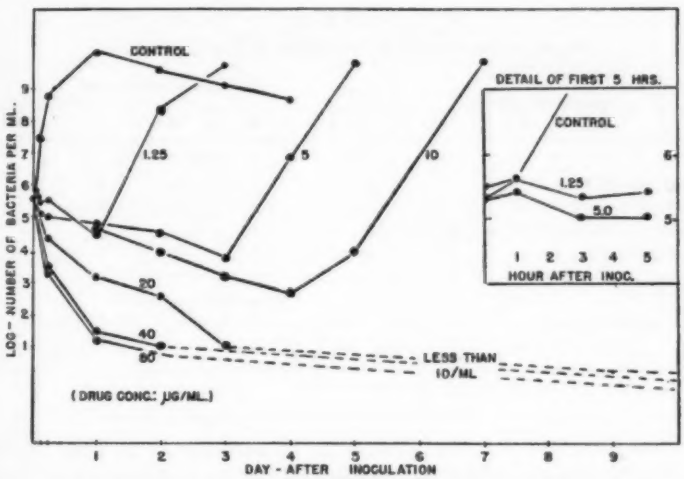

FIG. 1

Effect of terramycin hydrochloride on multiplication of *E. coli*.

In one experiment with 5 μg/ml terramycin the organisms which grew out on the fourth day were tested for sensitivity to the agent. They were inhibited by the usual 1.25 μg/ml, showing that outgrowth was not due to the emergence of resistant organisms. It seemed probable that it was caused by deterioration of the agent to a point where it was no longer capable of inhibiting *E. coli*. This possibility was tested by measuring the bacteriostatic activity of filtrates of a culture of *E. coli* in terramycin broth, daily until growth appeared. Controls consisting of a frozen solution and an uninoculated, but filtered,

broth solution of terramycin were included. The haemolytic streptococcus, C203, was used as the test organism. The results, shown in Table III, indicate that on the third day—the day before growth became visible in the inoculated tube—the terramycin concentration had fallen from 5 μg/ml to 1.25 μg/ml. This would have been just sufficient to inhibit *E. coli* had not deterioration proceeded at an accelerated rate during the next 24 hours. It is significant that deterioration was no greater in the presence of *E. coli* than in the uninoculated broth solution.

TABLE III

Progressive Deterioration of Terramycin HCL at 37° Centigrade

TERRAMYCIN SOLUTION	HOURS AFTER PREPARATION				
	0	24	48	72	96
	Assay—μg/ml				
Aquaeous—frozen	5	5	5	5	5
Broth—incubated at 37° uninoculated	5	5	1.25	1.25	.312
Broth—incubated at 37° inoculated with E. coli	5	2.5	1.25	1.25	.312
	growth (turbidity)				
	−	−	−	−	++++

Test organism for assays: β streptococcus C203.

Absorption and excretion. Titration of aureomycin in body fluids, by the biological method, is complicated by the fact that its activity is interfered with by serum as well as by exposure to heat and alkali. Terramycin also is interfered with by serum, but to a lesser degree. End points were 8 times higher in 50 per cent serum than in broth, but only 1½ to 2 times higher in 20 per cent serum. In performing bioassays for terramycin, therefore, it appears unnecessary to follow the technique devised by Tompsett, Shultz and McDermott (4) for penicillin assay, according to which 20 per cent serum is present in all of the tubes.

Two normal men were given 2 gm (8 capsules) of terramycin HCl by mouth. This amounted by 27.4 mg/kg in one instance and 21.5

mg/kg in the other. The subject that received the larger dose vomited at 45 minutes. Blood samples were taken and urine was collected according to the schedule indicated in Table IV. The gradual dilutions suggested by Tompsett and his associates were used in titrating the sera, and serial twofold dilutions were used for the urine samples. The dilutions were inoculated with a blood broth suspension of the haemolytic streptococcus, C203, and the tests were read after 20 hours incubation at 37 C.

TABLE IV

Serum Levels and Urinary Excretion of Terramycin HCL After Oral Administration in Man

TIME AFTER Rx	SERUM LEVELS		PERIOD AFTER Rx	URINARY EXCRETION			
	E.O.*	F.J.†		Conc. E.O.	Amt. E.O.	Conc. F.J.	Amt. F.J.
Hr.	*μg/ml*		*Hr.*	*μg/ml*	*mg.*	*μg/ml*	*mg.*
½	3.12	1.56	0–2¼	100	5.2	156	17.5
1	3.12	2.6	2¼–4	312	25.7	156	49.0
2	3.12	4.0	4–8	312	131.8	100	54.5
4	5.2	4.0	8–24	50	128.6	100	108.0
8	2.0	1.04	Total Excreted..		291.4		229.0
24	1.3	0.5	Per cent of Dose		14.6		11.4

* E. O. received 21.5 mg/kg.

† F. J. received 27.4 mg/kg; he vomited 45 minutes later.

As seen in Table IV, the peak serum level, 4 to 5 μg/ml, was noted at 4 hours in one instance and at 2 and 4 hours in the other. Readable amounts of terramycin were still present in the serum at 24 hours. Maximal excretion occurred after 4 hours, but appreciable amounts of the agent were excreted during the first 2¼ hours after administration. The concentration was still high in the 8 to 24 hour specimens of urine. From 11 to 14 per cent of the dose was recovered in the 24 hour period.

These figures are similar to those obtained by investigators at the Research Laboratories, Chas. Pfizer & Co. (5) in one of three subjects that received 25 mg/kg terramycin HCl per os. Two other subjects

had much higher serum levels and excreted 48 and 98 per cent of the dose in 24 hours. It is interesting that in the present study there

TABLE V

Control of Haemolytic Streptococcal, Pneumococcal and K. Pneumoniae Infections in Mice with Terramycin and Aureomycin

DOSE OF DRUG	PER CENT SURVIVAL (10-20 mice each group)			MEDIAN SURVIVAL TIME		
	Terramycin	Aureomycin	Controls	Terramycin	Aureomycin	Controls
Group A β Streptococcal Infection—Strain C203—100,000 MLD						
mg/kg/dose						
0	—	—	0	—	—	<24 hr.
2	0	10		38 hr.	53 hr.	
5	15	10		62 hr.	72 hr.	
10	0	30		64 hr.	6 days	
25	10	100		84 hr.	>14 days	
50	70	—		>14 days	—	
Type I Pneumococcal Infection—Strain SV1—10,000-100,000 MLD						
0	—	—	0	—	—	33 hr.
5	0	5		52 hr.	62 hr.	
10	0	10		59 hr.	63 hr.	
15	0	35		61 hr.	78 hr.	
20	—	100		—	>14 days	
25	10	100		62 hr.	>14 days	
50	100	—		>14 days	—	
K. pneumoniae Type A Infection—Strain KpnAD—10,000-50,000 MLD						
0	—	—	0	—	—	<24 hr.
10	10	—		36 hr.	—	
15	5	—		44 hr.	—	
20	60	—		>14 days	—	
25	70	0		>14 days	34 hr.	
50	—	10		—	<24 hr.	
75	—	40		—	120 hr.	
100	—	30		—	84 hr.	

Infections induced by intraperitoneal injection of organisms.
Rx: Subcutaneous injections at 0, 5½ and 23 hr. after infection.

was little difference between the responses of the two individuals in spite of the fact that one of them had vomited soon after taking the drug.

Therapeutic trials. The results obtained in the treatment of experimental infections in mice are shown in Tables V and VI. Terramycin was more effective than aureomycin in protecting mice against *K. pneumoniae* and *H. influenzae* but less effective against the haemolytic streptococcus and the pneumococcus.

TABLE VI

Control of Haemophilus Influenzae Infection in Mice with Terramycin and Aureomycin

Type B—Strain 641

DOSE OF DRUG	PER CENT SURVIVAL (10–20 mice each group)			MEDIAN SURVIVAL TIME		
	Terramycin	Aureomycin	Controls	Terramycin	Aureomycin	Controls
2,500,000 organisms						
mg/kg/dose						
0	—	—	0	—	—	<24 hr.
1	0	0		<24 hr.	<24 hr.	
5	0	0		<24 hr.	<24 hr.	
20	30	0		38 hr.	<24 hr.	
75,000 organisms						
0	—	—	5	—	—	<24 hr.
1	0	0		<24 hr.	<24 hr.	
5	0	0		<24 hr.	<24 hr.	
10	0	10		<24 hr.	<24 hr.	
15	0	—		36 hr.	—	
20	50	30		72 hr.	<24 hr.	
40	90	10		>8 days	<24 hr.	
800 organisms						
0	—	—	0	—	—	<24 hr.
1	0	0		<24 hr.	<24 hr.	
5	10	0		<24 hr.	<24 hr.	
20	90	10		>8 days	<24 hr.	

Infections induced by intraperitoneal injection of organisms in mucin.
Rx: Subcutaneous injections at 0, 5½ and 23 hr. after infection.

DISCUSSION

Terramycin appears to have an effect upon bacterial growth midway between the bacteriostatic action of the sulfonamides and the bactericidal action of certain of the antibiotics. In the case of penicillin, for example, at concentrations little above the minimal inhibitory

concentration there is a continuous decrease in population terminating in sterilization. Terramycin acts in much the same manner as aureomycin. In all but very high concentrations there is a slight decline in bacterial count, which may vary in duration from hours to days, after which multiplication begins. With terramycin, as with aureomycin, this eventual outgrowth seems most readily to be explained by the tendency of the drug to deteriorate at incubator temperature.

In spite of the fact that terramycin was only bacteriostatic in the test tube it proved to be an effective therapeutic agent in experimental infections. In this respect again it resembled aureomycin.

SUMMARY

Terramycin inhibited the growth of most of the bacteria tested at slightly lower concentrations than aureomycin.

Oral administration of a single dose of terramycin HCl to two human subjects resulted in measurable levels of the drug in the blood and urine for at least 24 hours.

Terramycin was more effective than aureomycin in the therapy of *K. pneumoniae* and *H. influenzae* infections in mice but was less effective in pneumococcal and haemolytic streptococcal infections.

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PHOSPHATASE ACTIVITY OF CARTILAGE AND PERIOSTEUM WITH VARIOUS SUBSTRATES*

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For the past few years we have been interested in obtaining information dealing with differences between chondroblastic activity and osteoblastic activity from the standpoint of matrix production and deposition of inorganic materials. For instance, in ascorbic acid deficiency growth of the cartilage and deposition of inorganic elements in the intercellular matrix take place in normal fashion; osteoblastic activity comes to a standstill, however (1). So too, it appears likely that the calcification mechanism differs in cartilage matrix and osteoid, the former depending perhaps on the glycogenolytic cycle (2), the latter on as yet unidentified mechanisms. In addition, cytochrome oxidase activity would appear to be absent in cartilage but present in osteoblasts and periosteum (3). Since phosphatase activity is relatively easy to measure in hypertrophic cartilage by chemical means and since quantitative data for the phosphatase activity of strips of periosteum can be obtained (4), it seemed worthwhile to compare these two kinds of tissue in order to ascertain whether any differences could be detected in their phosphatase activity on various substrates. Although a good deal of information is available on the activity of cartilage (and bone, including marrow elements), little attention has been paid to isolated periosteum.

Materials and Methods: Costochondral junctions were obtained from young growing dogs and new born infants at autopsy. A horizontal cut was made at the cartilage-shaft junction, not including any bone; a second cut was made 1 to 2 mm. above this in the cartilage. The resulting slices were cleaned of muscle, fat and perichondrium, weighed, and placed in a stainless steel receptacle immersed in an alcohol-carbon dioxide bath. The receptacle was fitted with a piston which was struck with a hammer in order to pulverize the brittle cartilage as finely as possible. Periosteum was stripped from the inner surfaces of the ribs after first

* Aided by grants from Mead Johnson and Company and the Damon Runyon Cancer Fund.

removing the pleura and any overlying fat. Such tissue was treated as above or, in some instances, homogenized, a procedure which cannot be applied to cartilage. The tissue preparations were suspended in water; toluene was added and they were allowed to stand at room temperature for 48 hours. The suspensions were then centrifuged and the supernatants removed. The following substrates were used: sodium glycerol-phosphate, glucose-1-phosphate*, glucose-6-phosphate*, hexose-di-phosphate*, phosphoglyceric acid[1], yeast nucleic acid (unheated and heated with IN HCl), sodium metaphosphate and sodium pyrophosphate. Each was added to veronal buffer, pH 9.0 and 7.4 and acetate buffer, pH 5.0. The phosphorylated sugars were present in concentrations of .01 M phosphorus; nucleic acid and the pyro and metaphosphates were present in concentrations of .1%. Tubes were set up containing: 1) substrate in buffer with tissue extract, 2) buffer alone with

TABLE I

*Phosphatase Activity of Cartilage and Periosteum with Different Substrates at Varying pH**

SUBSTRATE	CARTILAGE			PERIOSTEUM		
	8.9	7.4	5.0	8.9	7.4	5.0
Glycerol-phosphate	19.4	7.1	1.0	15.3	6.2	1.0
Glucose-1-phosphate	10.8	3.5	1.0	12.6	4.0	1.0
Glucose-6-phosphate	6.6	2.3	1.0	4.6	1.9	1.0
Phosphoglyceric acid	4.3	3.0	1.0	5.0	2.1	1.0
Hexose-di-phosphate	14.0	12.0	1.0	10.1	7.3	1.0
Sodium meta phosphate	1.2	1.0	4.5	1.0	1.4	3.1
Sodium pyrophosphate	1.0	2.0	4.0	1.0	3.7	8.8
Yeast nucleic acid	0	0	0	0	0	0
Yeast nucleic acid (depolymerized)	2.0	10.0	1.0	2.1	4.6	1.0

* See text for explanation.

tissue extract and 3) substrate in buffer alone. They were incubated at 37°C for 1 hour. The amount of inorganic phosphorus liberated was then determined and the final corrected value obtained after subtracting the amount present in tissue extract and substrate.

Results: The results of a number of determinations in the dog and human, though varying from specimen to specimen, have been consistent. A typical protocol for cartilage and periosteum from the same animal is shown in Table I. Since activity varies from preparation to

[1] Kindly furnished by Dr. Philip Handler, Department of Biochemistry, Duke University.

preparation the values which are given at each pH are relative ones to each other for each substrate. The lowest quantity of phosphorus liberated in micrograms after substracting the phosphorus present in the enzyme preparation and substrate is taken as unity and the higher two values are expressed in multiples of this. It is impossible to express phosphatase activity in cartilage on a weight basis since the amount of inactive tissue included varies from preparation to preparation. It will be noted that phosphatase activity of cartilage and periosteum are relatively the same for all the substrates studied. The phosphorylated hexoses, glycerol phosphate, and phosphoglyceric acid were all hydrolyzed maximally in alkaline medium and least at a pH of 5.0. In contrast it appears that both cartilage and periosteum have acid phosphatase activity on metaphosphate and pyrophosphate. In addition although undepolymerized yeast nucleic acid is not attacked, this material when depolymerized by heating with HCl may be dephosphorylated by what appears to be a phosphatase which has its maximum activity at neutral pH.

Discussion: Since Robison's (5) demonstration that bone contains an enzyme which hydrolyzes hexose-monophosphoric acid, the phosphatase activity of skeletal tissues has assumed a great deal of importance because of the possible role of this enzyme in the calcification mechanism. Quantitative observations were made by Robison (5, 6) using extracts of the costo-chondral junction, shaft of femur or epiphyseal cartilage as the source of enzyme and glycerol-phosphate, glucose-monophosphate, fructose-monophosphate, mannose-monophosphate and hexose-diphosphate as substrates. Robison (7) also found that the enzyme was most active at an alkaline pH. Hommerburg (8) using femoral epiphyses from various animals found that hexose-monophosphate and hexose-diphosphate were attacked. Liebknecht (9) utilizing rabbit bone reported that adenylpyrophosphate was partially hydrolyzed. Franseen and McLean (10) investigated the glycerol-monophosphatase activity of bone tumors; Gomori (11) using similar tissue used hexose-diphosphate as substrate. Woodard (12) has reported quantitative data on the activity of cortical and cancellous bone of children and adults, using glycerol-phosphate as the substrate. Gutman (13) has found that ground rat epiphyses hydrolyze glucose-1-phosphate and adenosinetriphosphate. We (4) have investigated gly-

cerol-phosphatase activity in relation to the morphological differentiation of cartilage and have also utilized strips of periosteum as a source of the enzyme to obtain quantitative data. Contributions dealing with the qualitative histochemical demonstration of phosphatase activity in skeletal tissues are summarized elsewhere (3).

From the results obtained in the present study it would appear that both hypertrophic cartilage and periosteum each contain phosphatases which attack similar substrates. The activity of the alkaline phosphatase of hypertrophic cartilage confirms the the findings referred to above. Periosteum likewise contains an alkaline phosphatase which acts on the same substrates as that from cartilage. The finding that cartilage and periosteum both contain an enzyme (or enzymes) which act on metaphosphate and pyrophosphate has not been reported heretofore. The significance of this observation is not at all clear. So too, the presence of an enzyme with optimum activity at neutral pH which acts on depolymerized yeast nucleic acid is of interest but of unknown significance at the present time. It would seem unwise to speculate on the role of these enzymes in either the calcification mechanism or the formation of cartilage or osteoid matrix. Current concepts (14) of the former with emphasis on the glycogenolytic cycle would appear to deemphasize the role of phosphatase. On the other hand the increasing interest on the relationship of phosphatase activity to the formation of fibrous proteins (15) and its disappearance and reappearance in absolute and healing scorbutus (16) do not make one want to relegate this enzyme to the background as far as its role in the formation cartilage and osteoid matrices is concerned.

Summary: Extracts of costochondral hypertrophic cartilage and periosteum were tested quantitatively for phosphatase activity at alkaline, neutral and acid pH using various substrates. No differences were found in the two types of tissue studied. It would appear that both cartilage and periosteum contain, in addition to "alkaline phosphatase," an acid phosphatase acting on meta and pyrophosphate as well as an enzyme attacking depolymerized yeast nucleic acid most readily in a neutral medium.

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THE ABILITY OF ACTH AND CORTISONE TO ALTER DELAYED TYPE BACTERIAL HYPERSENSITIVITY*

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INTRODUCTION

Although considerable knowledge of the various human endocrine functions has resulted from the application of Cortisone (11 dehydro-17 hydroxycorticosterone) and adrenocorticotrophic hormone (ACTH) to the spectrum of human ailments (1–5), little is known about their mode of action. At least two types of alteration in the host accompany treatment with these compounds: 1. There is a profound effect upon the lymphoid system, and by implication, upon its function in immunological processes, and 2. There is an equally striking effect upon many biochemical phenomena, for example, the inhibition of mitotic cell division (6) in separate parts of the body.

The first of these alterations, the effect on the structure and function of lymphoid tissue, has been extensively studied. Morphological changes in lymph nodes (7), and changes in the peripheral lymphocyte count have been seen (8). In addition, certain variations in serum proteins have been observed; for example, a fall in the antistreptolysin titer (9), serum complement and gamma globulin content of serum during hormone treatment have been noted (10). These findings, together with the studies recently reported concerning the effect of ACTH on anaphylactic allergy (11), further support the basic effect of these substances on immune mechanisms. The present report indicates that equally striking alterations in tuberculin type allergy may be seen during ACTH and Cortisone treatment.

MATERIALS AND METHODS

Tuberculin. Purified protein derivative, PPD (12), 0.02 gamma (first strength) or 5 gamma (second strength) in 0.1 ml. of buffered saline, was injected intra-

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dermally on the volar surface of the forearm. This material was chosen because of its high degree of specificity, and because a majority of adults will show a positive reaction to one or the other of these two dilutions, independent of the disease processes being treated.

Beta hemolytic streptococcus vaccine. A Beta hemolytic streptococcus, BHS, suspension was used as a skin test control. One tenth ml. buffered saline suspension containing approximately 9×10^8 per ml. organisms was given intradermally concomitantly with the PPD tests. The testing suspension was made of a stock strain of Beta hemolytic streptococci previously found to produce a delayed type skin reaction in persons with clinical and bacteriological evidence of a recent Beta hemolytic streptococcal infection. Cultures were grown for 48 hours in tryptic digest broth and washed three times by centrifugation in physiological saline before the final cell concentration was adjusted. The organisms were killed by heating the final suspension in a water bath at 56° C. for 30 minutes. Sterility was determined with 1 ml. aliquots planted in thyoglycolate broth. The vaccine was stored at 4° C. when not in use. Under these circumstances similar vaccines have been found to give uniform skin test results for periods up to four months, the time during which this study was carried out.

So far as possible, serial tests on each patient were done with a single lot of material. In many instances, multiple tests on the same individual with different vaccine lots were found to give essentially similar results.

Histamine. Histamine phosphate 1.0 mg. per ml. as supplied in commercial ampules was freshly diluted 1:10, 1:100 and 1:1000, and 0.1 ml. of each dilution injected intradermally.

Intradermal reactions. The histamine reaction was used as the prototype of immediate hypersensitivity, in contrast to the PPD and BHS reactions, which were chosen as models of delayed type hypersensitivity. The delayed type intradermal reaction varies greatly in appearance, sequence of development, and duration, depending upon the nature of the testing material and the sensitivity of the patient. In our experience, a minimal reaction to PPD is regarded as any measurable area of erythema which reaches maximal development in 12 to 24 hours and disappears in 48 hours. A more intense tuberculin reaction exhibits central induration with surrounding erythema, and reaches its maximal size in 24 to 48 hours. A markedly positive reaction, in which central necrosis occurs, may not reach its height for 48 hours or longer, and may continue to exhibit inflammatory changes for several days.

The BHS reaction exhibited all of the characteristics commonly ascribed to the delayed type tuberculin reaction, in that a minimal response consisted of erythema, while induration and necrosis accompanied the severe reactions. It was more common to observe a relatively larger area of erythema in proportion to the area of induration, but whenever present, the obvious areas of induration and necrosis were also measured.

For the purposes of this study the PPD or BHS reaction has been designated as "obliterated" when it exhibited no erythema after the initial traumatic effect of the injection had disappeared. No matter how slight, areas of erythema or

induration, appearing 10 to 48 hours after the intradermal injection of antigen, have been considered to be positive reactions. Variations from the normal not meeting these criteria were considered to be "altered."

Histamine reactions were observed at 5 and 20 minutes. The area of whealing and erythema resulting from each dilution employed was measured.

Clinical Material. During the latter part of 1949, and the early part of 1950, ACTH and Cortisone were released for human use in many pathological states. The availability of patients under study offered an opportunity to observe the effects of treatment on intradermal reactions. At first, observations were made at random points during the course of treatment. It soon became apparent that the most useful information was to be derived from individuals who received relatively large doses of hormone treatment continuously for a period of several weeks.

A selected group of 35 treated patients are considered in this report (Chart 1). All but one received either ACTH (45 mgm. to 200 mgm.) for 7 to 90 days, or Cortisone (100 mgm. to 200 mgm. a day) for 7 to 40 days. The one exception was a patient, who had a spontaneous Cushing's syndrome, who was tested before and after successful radiation therapy to the pituitary gland.

Twelve patients hospitalized for rheumatoid arthritis, who served as clinical controls, received neither ACTH nor Cortisone. They were skin tested at the same intervals with the same materials used in the treated subjects.

RESULTS

Tuberculin Reactions (Chart I): Group I, Chart I, lists ten patients tested before, during and after hormone treatment. These patients received 21 days' treatment. Five were given Cortisone, 100 mgm. per day, one was given Cortisone, 150 mgm. per day, and the remaining four received from 40 mgm. to 112 mgm. of ACTH daily. Before treatment, each of these patients had a positive PPD reaction. During therapy, the skin reaction to new tests was significantly diminished, the test being obliterated in four of the ten patients between the tenth and twenty-first day. Following treatment, a return of the hypersensitivity reactions to a new skin test occurred in each patient tested.

Group II, Chart I, is made up of five patients who received ACTH in doses varying from 40 mgm. to 100 mgm. daily for periods ranging from one to three weeks. Each of these patients exhibited a negative tuberculin reaction before, during, and after treatment.

Group III includes patients with wide variations in time and dosage schedules. Seven patients received an average per patient dose of ACTH varying from 40 mgm. to 100 mgm. daily for periods ranging from one to twelve weeks. The other two patients, case numbers 16 and 24, received Cortisone and ACTH as explained below. All of the patients in this group demonstrated obliteration of the PPD reaction at some period of their course of hormone treatment. Patient number 16 received a 21-day course of Cortisone, 100 mgm. daily and then a 14-day course of ACTH, 45 mgm. daily. The PPD reaction was obliterated during the second week of therapy. A positive reaction failed to appear 37 days after the cessation of treatment. At the time of writing, this patient was receiving another course of Cortisone therapy and the PPD reaction was still obliterated.

Patient number 24 received 21 days of Cortisone with little alteration in the PPD reaction. This same patient subsequently received a second 10-day course of treatment (four days of ACTH, 40 mgm. daily and six days Cortisone, 100 mgm. daily), at the end of which the PPD reaction had been obliterated.

Four of the nine patients in Group III, who received doses of ACTH varying from 50 mgm. to 100 mgm. per day, demonstrated obliteration of the skin tests during the first week of treatment. Those patients in this group whose treatment was stopped regained the ability to have a positive PPD reaction. It should be noted that in case number 17, this reaction became positive during a long tapering off course at a greatly reduced dosage.

Group IV includes 7 patients treated with ACTH, and one patient treated with Cortisone. The dosage of Cortisone was 150 mgm. per day for 7 days; the average dosage of ACTH varied from 30 mgm. to 100 mgm. daily for 7 to 21 days. In contrast to the cases collected in Group III, none of these patient's reactions were obliterated in the first week of treatment despite a dose of hormone that was on the average higher than that in the former group. Case number 28 was the only one who received more than two weeks of treatment, and

CHART I

Tuberculin Reactions

GROUP	NO.	PATIENT	MEDICATION		DAYS OF TREATMENT	DISEASE	INTRADERMAL REACTIONS ACCORDING TO TREATMENT DAYS											
							Before		7		14		21		30–		After	
			ACTH	Cortisone			I	E	I	E	I	E	I	E	I	E	I	E
I	1	V. A.		100 mgm	21	Rheumatoid A.	10	15			0	0	0	0			23	37
	2	L. C.		150	21	Scleroderma	18	20			0	0	0	0			0	25
	3	E. T.	112 mgm		21	Rheumatic F.	7	23			0	0	0	0			0	20
	4	G. C.		100	21	Rheumatoid A.	10	20			0	7	0	0			10	35
	5	C. C.	80		21	Mult. Myeloma	0	13			0	0					0	4
	6	E. A.	50		21	Rheumatoid A.	10	15			0	15	0	8			12	25
	7	N. H.		100	21	Rheumatoid A.	0	20			0	30	0	15			0	40
	8	H. B.		100	21	Rheumatoid A.	8	15			0	40	0	30				
	9	M. G.		100	21	Rheumatoid A.	10	25			0	30	0	18			4	20
	10	H. C.	40		21	Rheumatoid A.	20	40			15	45	5	40			20	110
II	11	A. M.	75		15	Ulc. Colitis	0	0	0	0	0	0					0	0
	12	P. O'B.	75		17	G-nephritis	0	0	0	0	0	0					0	0
	13	E. B.	40		23	Rheumatoid A.	0	0	0	0	0	0	0	0			0	0
	14	B. G.	60		23	Rheumatoid A.	0	0					0	0			0	0
	15	M. A.	100		10	Lupus E.	0	0									0	0
III	16	D. W.	45(14d)	100(21d)	35	Dermatomyositis	0	20			0	0	0	0				
				79	55										0	0		
	17	O. O'D.	100		28	Ulc. Colitis			0	0	0	0			0	30	10	65
	18	G. D.	95		7	G-nephritis	0	10	0	0							0	4
	19	F. B.	40		17	Inf. Hepatitis			0	0	0	0					0	5
	20	G. J.	80		90	Lupus E.									0	0	0	0

	21	B. R.	50		7	Rheumatoid A.			0	0						4	110
	22	R. S.	40		21	Scleroderma					0	0				0	18
	23	D. B.	40		54	Lupus E.							0	0		2	25
	24	Q. A.		100	21	Rheumatoid A.	2	12			12	30	5	20			
			40(4d)	100(6d)	10				0	0						0	35
IV	25	M. A.		150	7	G-nephritis	0	25	0	10						16	67
	26	B. V.	30		7	Lupus E.			0	20							
	27	A. N.	40		10	Rheumatoid A.	4	20	0	20						5	30
	28	Y. H.	100		29	Rheumatoid A.	10	35			0	30	0	18			
	29	M. R.	65		13	Mal. Exoph.	30	50	25	45	10	20					
	30	T. O'T.	100		7	G-nephritis	0	12	8	35							
	31	J. P.	100		7	G-nephritis	20	20	10	35							
	32	K. B.	100		8	Thyroiditis	5	20	2	20						0	15
V	33	C. J.	125(29d)	100(15)	44	Thyrotoxicosis					12	12	10	15	0	4	
	34	I. M.	110		13	Thyrotoxicosis	20	40	15	30	0	35					
VI	35	E. H.	Pituitary x-ray therapy		25	Cushing's Dis.	0	0	0	20	0	30				5	40

although the reaction had been altered by the third week of treatment, it was not obliterated.

The two cases in Group V have been set apart because of other studies (13) which indicate that patients with untreated thyrotoxicosis are more sensitive reactors to delayed type skin tests. Case number 33 received 100 mgm. of Cortisone daily for 15 days and then an average dose of 125 mgm. of ACTH daily for 29 days. Although it was not possible to test this patient before treatment, it should be noted that no other patient presented in this chart was so retarded in exhibiting an altered PPD reaction. The companion case, number 34, received 110 mgm. of ACTH for 13 days. During the second week the induration disappeared, and the erythema became larger, more diffuse, and less dusky than it had been during the first week of treatment. This pattern has been observed repeatedly in highly sensitive reactors.

Streptococcal Reactions (Chart II): Chart II is a presentation of the parallel intradermal reactions to the streptotoccus antigen exhibited by the patients considered in Chart I.

The two cases in Group V are examples of a return of the BHS reaction during treatment. Although a Beta streptococcus organism was not recovered by nose or throat culture, each one of these patients had an upper respiratory infection at the time.

The BHS reaction of the patient in Group VI became positive at the end of the first week of x-ray therapy.

A review of Charts I and II indicates that individuals who lost one type of skin reaction did not necessarily lose both reactions, nor did degrees of alteration under therapy uniformly parallel each other.

Histamine Reactions. Eight patients receiving either Cortisone or ACTH were tested intradermally with histamine at random intervals during their course of treatment. Four patients with rheumatoid arthritis not receiving hormone therapy were similarly tested. A typical flare, flush and wheal were observed in both treated and untreated patients at the end of 10 and 20 minutes.

Control Intradermal Reactions (Chart III): Chart III displays the results of skin tests with the same antigens in 12 untreated patients with rheumatoid arthritis. Intradermal reactions were placed at approximately 7 day intervals for a minimum of 5 to a maximum of 12 weeks.

The size of the reactions varied widely from week to week. Negative intradermal BHS reactions occurred in the two least "sensitive" reactors (Case numbers 4, 10), in this group on one occasion, but returned the following week. A negative tuberculin reaction occurred in the ninth consecutive week of testing in case number 11, whose reactions were unremarkable for their erythema and induration. That this is not simply a factor of the number of repetitions is demonstrated by the patient tested 12 weeks, in whom there was a constant variation in the character and size of the reactions.

As further evidence of the body's altered immunologic reaction while under the influence of excess adrenal cortical hormone secretion, 3 cases are presented in detail.

The first patient, (Case number 10, Chart I), a 38-year old, 159-pound male with rheumatoid arthritis of 9 years' duration, had a marked systemic as well as a 4+ necrotizing local reaction to the tuberculin test before treatment. There was an associated fever of 102.8°, as well as a feeling of general malaise, beginning approximately 8 hours after intradermal inoculation. Within 24 hours, a chestnut-sized tender axillary lymph node could be palpated. The temperature subsided in 4 days, and the gland in 6 days.

This test was repeated after 10 days of ACTH, 40 mgm. per day. The tuberculin reaction was as large, but was graded 3+ because the marked induration did not go on to hemorrhagic necrosis as it had done before treatment. There was no lymphadenopathy. The temperature which had been rising daily to 99.6° reached 102° approximately 12 hours after the skin test had been placed and was accompanied by headache, chills and malaise. The patient was asymptomatic within 24 hours.

At the end of 20 days ACTH, the test was repeated, and on this occasion, we observed a 2+ area of induration with much less erythema. There was no evidence of systemic manifestations.

Eight days after the ACTH therapy had been completed, this patient exhibited a 4+ hemorrhagic area of hypersensitivity, which consisted of a dusky erythema measuring 110 mm. in diameter with a 20 mm. central vessicle. Although there had been no elevation in temperature concomitant with the skin test on the twentieth day of treatment, the temperature this time rose to 101° within 6 hours, and reached 103° within 24 hours. Physical examination failed to reveal any other etiology for this fever.

The Beta streptococcal intradermal test in this individual was recorded as 20 mm. of erythema before treatment. On the tenth day of treatment, it measured 15 mm. of erythema and on the twentieth day, 4 mm., which is considerably less than the arbitrary standard of 10 mm. usually fixed for a 1+ reaction. Eight days later, although the tuberculin test had returned to its previous status as

CHART II

Beta Hemolytic Streptococcus Reactions

GROUP	NO.	PATIENT	MEDICATION		DAYS OF TREATMENT	DISEASE	INTRADERMAL REACTIONS ACCORDING TO TREATMENT DAYS											
							Before		7		14		21		30-		After	
			ACTH	Cortisone			I	E	I	E	I	E	I	E	I	E	I	E
I	1	V. A.		100 mgm	21	Rheumatoid A.	10	40			0	30					15	53
	2	L. C.		150	21	Scleroderma	10	35			0	20	0	10			10	30
	3	E. T.	112 mgm		21	Rheumatic F.	15	33	0	15	0	20	0	12			4	55
	4	G. C.		100	21	Rheumatoid A.	0	30			0	10	0	20			0	15
	5	C. C.	80		21	Mult. Myeloma	10	10			0	4	0	0			0	7
	6	E. A.	50		21	Rheumatoid A.	0	25			0	3	0	5			0	15
	7	N. H.		100	21	Rheumatoid A.	0	30			0	0	0	0			0	5
	8	H. B.		100	21	Rheumatoid A.	0	30			0	25	0	20				
	9	M. G.		100	21	Rheumatoid A.	10	25			0	35	0	6			10	30
	10	H. C.	40		21	Rheumatoid A.	0	20			0	15	0	4			0	20
II	11	A. M.	75		15	Ulc. Colitis	0	10	0	0	0	0	0	0				
	12	P. O'B.	75		17	G-nephritis	0	20	0	5	0	12					11	32
	13	E. B.	40		23	Rheumatoid A.	0	20	0	0	0	0						
	14	B. G.	60		23	Rheumatoid A.							0	0			0	25
	15	M. A.	100		10	Lupus E.			0	0							0	30
III	16	D. W.	45(14d)	100(21d)	35	Dermatomyositis	0	45			0	10	0	4	0	0		
				79	55										0	0		
	17	O. O'D.	100		28	Ulc. Colitis			0	0	0	0			0	10	0	15
	18	G. D.	95		7	G-nephritis	0	18	0	0							0	15
	19	F. B.	40		17	Inf. Hepatitis					0	0	0	0			0	10
	20	G. J.	80		90	Lupus E.									0	0	0	18

	21	B. R.	50		7	Rheumatoid A.			0	0							0	10
	22	R. S.	40		21	Scleroderma							0	0			0	25
	23	D. B.	40		54	Lupus E.									0	0	0	35
	24	Q. A.		100	21	Rheumatoid A.	0	15	0	0	0	0					0	4
			40(4d)	100(6d)	10				0	0								
IV	25	M. A.		150	7	G-nephritis	12	110	0	12							6	52
	26	B. V.	30		7	Lupus E.	0	20	0	15								
	27	A. N.	40		10	Rheumatoid A.	0	25	0	0							0	10
	28	Y. H.	100		29	Rheumatoid A.	0	25			0	4						
	29	M. R.	65		13	Mal. Exoph.	0	20	0	12	0	4						
	30	T. O'T.	100		7	G-nephritis	10	30	0	0								
	31	J. P.	100		7	G-nephritis	4	15	0	15								
	32	K. B.	100		8	Thyroiditis	0	20	0	4							0	12
V	33	C. J.	125(29d)	100(15)	44	Thyrotoxicosis					0	0	0	15	0	0		
	34	I. M.	110		13	Thyrotoxicosis	5	25	0	0	0	3						
VI	35	E. H.	Pituitary x-ray therapy		25	Cushing's Dis.	0	0	0	25	0	20					0	0

CHART III

Beta Streptococcus Reactions—Control Group

	NAME OF PATIENT	NUMBER OF TEST IN WEEKS																							
		1		2		3		4		5		6		7		8		9		10		11		12	
		I	E	I	E	I	E	I	E	I	E	I	E	I	E	I	E	I	E	I	E	I	E	I	E
1	W. H.	0	5	0	2	0	25	0	16	15	30														
2	D. G.	0	25	0	5	0	24	26	51	10	40	10	35												
3	G. B.	0	18	0	40	0	43	0	47	10	25	12	45												
4	D. C.	0	20	0	4	10	30	0	0	0	30	0	10												
5	F. F.	10	30	0	19	0	38	10	40	20	40	10	60	10	50										
6	H. C.	0	10	15	40	16	60	55	69	15	45	15	60	10	45	10	40								
7	O. H.	0	30	0	15	0	24	16	46	20	50	15	50	0	51	10	53								
8	S. O.			5	30	0	35	43	50	0	20	10	25	0	40	10	30								
9	D. G.	0	8	0	15	0	10	0	6	17	25	0	26	0	20	0	15	0	23	0	20				
10	D. M.	0	10	0	15	0	10	0	0	0	32	0	29	0	25	0	20	0	10	0	10				
11	G. C.	20	40	0	10	0	15	0	15	0	7	0	10	0	7	0	5	17	31	16	36				
12	R. L.	0	35	0	20	0	30	0	15	0	12	0	10	0	0	0	15	15	35	0	25	10	61	10	50
	Tuberculin Reactions—Control Group																								
1	W. H.	10	20	18	20	11	43	17	31	15	30														
2	D. G.	0	15	0	10	10	30	17	20	10	20	0	10												
3	G. B.	0	5	0	15	23	23	25	25	0	20	0	10												
4	D. C.	8	25	4	12	6	25	4	20	10	20	2	20												
5	F. F.	0	4	0	4	0	12	0	10	0	15	0	12	0	10										
6	H. C.			0	5	20	32	17	20	0	35	0	15	0	25	0	10								
7	O. H.	0	10	0	10	19	21	15	45	7	20	10	30	0	45	0	20								
8	S. O.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0								
9	D. G.	0	7	15	55	0	20	0	4	19	40	0	31	0	15	0	7	0	10	0	10				
10	D. M.	0	12	0	12	8	30	25	30	12	21	17	17	12	30	10	24	0	10	0	18				
11	G. C.	15	20	8	15	4	10	4	12	10	20	12	16	4	5	0	7	0	0	19	23				
12	R. L.	2	12	2	12	5	25	5	30	10	12	5	8	0	7	0	20	0	10	0	8	0	10	0	12

described above, the Beta streptococcal sensitivity as measured by the skin test was zero. This patient was tested two months later and found to have a 10 mm. streptococcal response.

The second patient, (Case number 35), is that of a 38-year old female with fully developed Cushing's Syndrome, including round facies, striae, hypertension and mental dullness who had negative skin tests upon admission. After 11 days of pituitary fossa x-ray therapy, repeat skin tests showed a 20 mm. PPD and a 15 mm. BHS reaction. At the end of 19 days of radiation, the PPD measured 30 mm., and the BHS, 20 mm.

The pre-treatment fasting blood sugar of 290 mgm. per cent fell to 156 mgm.% at the end of 13 days of therapy. The absolute eosinophil count rose from 19 to 37, and the 17 keto-steroid excretion in 24 hours decreased from 19 to 14 mgm. Clinically, the patient was much improved.

The third patient, (Case number 34), a 29-year old male with thyrotoxicosis was selected for study because of our interest in the effect of this disease upon delayed skin reactions.

The initial second strength PPD test produced 40 mm. of erythema with a central area of induration, 20 mm. in diameter. The BHS reaction measured 25 mm. At the end of 8 days treatment, during which the patient received ACTH, 200 mgm. per day, the BHS skin test was negative, but the tuberculin test measured 25 mm. by 30 mm., and was less dusky red and less indurated. After 13 consecutive days of the same dosage, the tuberculin reaction had been altered once more, but still not obliterated. It now measured 20 mm. by 35 mm. and was flat and pink without induration. The BHS reaction previously recorded as 0 mm. measured 3 mm. Although a streptococcus was not recovered by nose and throat culture, the patient did have an upper respiratory infection at the time of this test.

Another patient with clinical thyrotoxicosis received 44 days of hormone therapy, including several days of both Cortisone and ACTH, before the skin tests were significantly altered. Even at this point, although the BHS test was obliterated, the tuberculin test measured 7 mm.

As a final commentary on the ability of ACTH to alter the intradermal evidence of hypersensitivity, there may be reported a series of delayed type bacterial skin tests which were placed in a patient under treatment for iritis. Three days after receiving 15 days of ACTH treatment, all of the skin tests became as intensely red and indurated as they had been prior to treatment. At the same time the patient's eye symptoms and signs returned. She was then given two more days

of ACTH. Within 18 hours the skin reactions promptly faded only to return once more, in a lesser degree, when ACTH was again discontinued.

Response to Hormone Treatment. The patients reported in this paper exhibited a fall in their eosinophile counts and a rise in their 17 ketosteroid excretion during treatment. Those receiving Cortisone usually responded to either a 4 hour or a 48 hour ACTH test. In a representative group of these patients, there was a lowering of the gamma globulin and complement levels during treatment in those diseases in which the pre-treatment levels were above normal. A high percentage fall in the eosinophiles did not herald an early disappearance of the intradermal tests, nor was there a direct correlation between the time of lowering of the gamma globulin titre and the negative skin reactions.

DISCUSSION

This report describes the changes in the intradermal skin reaction to tuberculin (PPD) and a Beta hemolytic streptococcal vaccine (BHS) produced by ACTH and Cortisone treatment. It has been found that a consistent decrease in the induration and, when present, the necrosis of these skin reactions, occurs during this form of treatment. The complete abolition of the intradermal reaction is more difficult to produce. Following therapy, the ability to have positive delayed type skin reactions is regained. Positive histamine skin tests occurred in both treated and non-treated patients.

For the purposes of this study, all reactions, whether induration or erythema only, have been considered specific tuberculin type reactions. Any erythema or induration occurring after the tenth hour has been considered significant. Using these criteria, it has been found that the most readily altered phase of the tuberculin type reaction is the prevention of necrosis. The next alteration is the prevention of induration, and finally, sufficient therapy may completely abolish erythema. The size of the zone of erythema does not diminish until the skin test is abolished. When systemic symptoms accompany a tuberculin reaction, they are well controlled by hormone therapy.

Of special interest in many patients was the lighting up of a diminished or completely obliterated skin reaction within 36 hours after

the cessation of treatment. In some instances these reactions went on to necrosis, even though the testing material had lain dormant in the skin for more than a week. When treatment was re-instituted, such rebound reactions promptly subsided, only to return again if treatment was not continued for a week or more. Deposits of skin testing material older than three weeks usually did not demonstrate these phenomena. Skin tests planted shortly after treatment were occasionally larger than those obtained before treatment.

The ability of ACTH and Cortisone to alter this delayed type bacterial allergy did not correlate directly with alterations in gamma globulins in the serum, the time of decrease of the sedimentation rate, or the response to intradermal histamine.

The significance of these findings is not yet clear. It is entertaining, and perhaps, useful, to point out some related information about the tuberculin reaction which has been presented by this and other laboratories in the past. The key to the delayed type tuberculin allergy is the leukocyte. In tissue culture (14), by passive transfer (15) and by direct study in mobile cell systems (16–18), tuberculin has a specific cytotoxic effect upon leukocytes. So far as is known this is unrelated to histamine. It is also this cell type which is immediately vulnerable to Cortisone and ACTH treatment, especially the small mature lymphocytes which have been thought to be most concerned with the tuberculin effect.

Another interesting facet of the tuberculin reaction is the role of tissue affinity for tuberculin (20). Observations made on these patients indicate that tissue holding of tuberculin continues during hormone treatment. Rebound reactions following treatment conceivably represent the return of sensitized lymphocytes to the body fluids.

It might be expected, therefore, that in those conditions in which tuberculin is being continually supplied in excess of its rate of destruction by immune processes, as for instance in active tuberculosis, an explosive systemic reaction should follow cessation of hormone treatment. The hope of using these drugs for the treatment of the tuberculous patient, which this and other studies (21) may raise, should be tempered by the realization that hormone treatment can indeed be a double-edged weapon.

Finally, these studies suggest possible explanations for relapses

which are being seen in many of the conditions which have responded initially to this form of treatment. Unless alteration of tissue affinities and control of the sources of possible antigens is feasible during specific hormone treatment, no permanent benefit from these hormones should be expected.

SUMMARY

1. The ability of ACTH and Cortisone to alter delayed type bacterial hypersensitivity has been observed in 34 treated patients.

2. The PPD (tuberculin) reaction was obliterated in 13, and the BHS (Beta hemolytic streptococcus) reaction obliterated in 19, of the 34 patients reported. In 7 of the 34 tuberculin tested and in 8 of the 34 streptococcus tested patients initial tests before treatment were not available.

3. The time of obliteration of these reactions varied from 3 to 30 days and was affected by the patient's initial degree of sensitivity, the dosage of hormone and the duration of treatment.

4. Those patients in whom these reactions were not obliterated showed a significant alteration of the induration and erythema in one or both intradermal tests.

5. Patients available for new intradermal tests after hormone therapy usually displayed a return of the ability to have positive PPD and BHS reactions 7 to 28 days after treatment.

6. Delayed type PPD and BHS reactions observed in 12 control patients during the same period showed wide variations in induration and erythema from week to week.

7. Normal histamine reactions were observed in treated and untreated patients.

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STUDIES OF THE METABOLISM OF THE HUMAN PLACENTA

II. Oxygen Consumption and Anaerobic Glycolysis in Relation to Aging and Severe Toxemia

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Probably the most widely held theory concerning the etiology of acute hypertensive toxemia in pregnancy is that of uterine and placental ischemia. This theory was first enunciated by James Young in 1914 (1) and has been sponsored by Beker (2), Dexter and Weiss (3), Page (4), Dieckmann (5) and many others. The recent development of the ischemia principle and its relation to hypertension is but a natural corollary to the work of Goldblatt (6) on the production of hypertension in dogs by means of renal ischemia. Certainly it is possible that a decrease in placental circulation could readily occur in certain conditions which are commonly associated with acute toxemia, namely, primiparity, multiple pregnancy, hydramnios, and hydatid mole. Furthermore, from the theoretical viewpoint it is quite possible that ischemia of the placenta could cause this organ to release some pressor substance into the maternal circulation. Diligent search for such pressor substances has been made, but none has yet been found. Page (7) has hypothesized that the pathological lesions in the liver could be caused by the release of thromboplastin from the ischemic placenta. This hypothesis is given additional weight by the finding of an increase in circulating cephalin in eclampsia (8) and by the demonstration of Copley (9) and Schneider (10) of large amounts of thromboplastin in the placenta. Although the entire theory of placental ischemia is attractive it has by no means been proved and the experimental proof that constriction of the uterine arteries does cause hypertension is fragmentary and not altogether convincing.

Nevertheless certain microscopic changes of the placental villi in toxemia have been described by Tenney and Parker (11) and changes in chemical morphology have been defined by Wislocki and Dempsey

(12). These changes could indicate either early aging or chronic ischemia of the placenta or both. In this laboratory the microscopic findings of Tenney have not been found with any degree of consistency in acute toxemia and we were thus led to approach this problem through a study of the changes of the metabolism of the placenta. On a theoretical basis, ischemia of the placenta could produce changes in the epithelial covering of the villi which if not visible microscopically should at least be discernible through metabolic studies in the Warburg apparatus. It was such reasoning that led Goldblatt (13) to study kidney slices from dogs rendered hypertensive by means of a Goldblatt clamp. Although he demonstrated a definite decrease in the oxygen uptake of these slices, this work was not confirmed by Mason, Robinson and Blalock (14). These latter investigators showed that Q_{O_2} and aerobic glycolysis in such slices were within normal limits. In spite of these latter findings, however, it seemed worthwhile to investigate the oxygen uptake and the anaerobic glycolysis of the placenta in patients suffering from severe and unquestionable acute toxemia of pregnancy.

The oxygen consumption of the human placenta has previously been studied in two ways. Perfusion of the organ with blood containing a known amount of oxygen was performed during the twenties by three separate German investigators (15, 16, 17) with inconstant results. Loeser (18) studied the oxygen uptake of the placenta in the Warburg apparatus and this work was further carried out by Wang (19) who demonstrated a progressive decrease in the oxygen uptake of the human placenta during the course of pregnancy. These results have been confirmed by Page (7).

Loeser (18) was the first to study the carbohydrate metabolism of this organ by the Warburg technique. He found that the younger the placenta the greater was the production of lactic acid in an anaerobic vessel.

Page (7) has recently stated that in placentas of patients suffering from acute toxemia there was a decrease in oxygen uptake, over and above that expected in the natural course of aging.

The oxygen consumption of the placenta was studied in 75 patients. Sixty-one came from clinically normal patients; two from patients suffering from chronic hypertensive vascular disease; eleven from moth-

ers having severe, acute toxemia and one from an eclamptic. In the normal group delivered at term or slightly prematurely, delivery was accomplished either per vaginum or by cesarean section. In the latter cases the reason for the operation was purely obstetrical and could not have influenced the function of the placenta. The more premature placentas were obtained from patients undergoing hysterotomy and suffering from diseases, which to all intents and purposes, could not have affected the placenta; these were, tuberculosis, chronic renal disease, cardiac disease, and in one instance, chronic hypertensive disease. The patients with severe, acute toxemia all had blood pressures of 160/100 or higher. Albumin was present in the urine and there

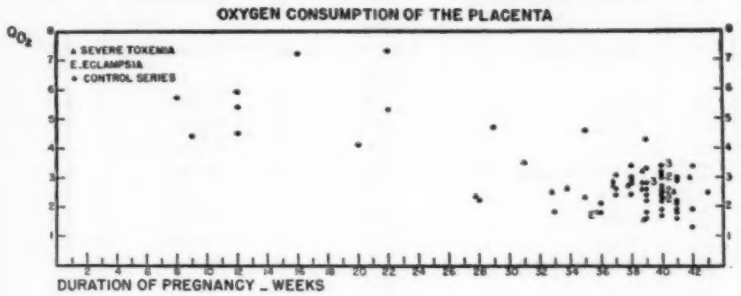

FIG. 1

was no evidence of pre-existing hypertensive disease. These patients were delivered in the acute phase of their toxemia and none had had hypertension for more than 3 weeks. The placentas were all obtained immediately following delivery. A large piece was cut off and placed in phosphate Ringer's solution. It was then brought to the laboratory where a few smaller pieces of tissue were dissected away. The chorionic and decidual plates were excluded. Areas of infarction, fibrosis and calcification were avoided. Small pieces of tissue were then prepared by cutting and teasing in phosphate Ringer's solution until each tiny piece contained only a few separated villi. These bits of tissue were suspended in 2.7 per cent phosphate Ringer's solution at a pH of 7.4 in a standard Warburg flask. In all instances 2 mg. of glucose were added to each cc of phosphate Ringer's solution. Carbon dioxide

TABLE I

Oxygen Consumption of the Placenta Control Series

NO.	MATERNAL DIAGNOSIS	BABY WEIGHT OR MEASUREMENT	DURATION OF PREGNANCY	TYPE OF DELIVERY	Q_{O_2}
		cm.	*weeks*		
1	Heart disease	C.R. 2.1	8	Hysterotomy	5.7
2	Heart disease	C.R. 2.75	9	Hysterotomy	4.4
3	Tuberculosis	C.R. 6.5	12	Hysterotomy	4.5
		grams			
4	Chorea	60	12	Hysterotomy	5.4
5	Chronic hypertension	40	12	Hysterotomy	5.9
6	Psychosis	Unknown	16	Hysterotomy	7.2
7	Chronic hypertension	Unknown	20	Hysterotomy	4.1
8	Chronic hypertension	Unknown	22	Hysterotomy	7.3
		cm.			
9	Heart disease	C.R. 18.5	22	Hysterotomy	5.3
		grams			
10	None	980	28	Vaginal	2.2
11	None	1015	29	Vaginal	4.7
12	None	1537	31	Vaginal	3.5
13	Premature separation	1700	33	Section	1.8
14	None*	2460	35	Vaginal	4.6
15	None*	2430	35	Vaginal	2.3
16	None	2360	36	Vaginal	2.1
17	Placenta previa	2480	36	Section	1.8
18	None	2390	37	Vaginal	2.6
19	Chronic nephritis	2470	37	Section	2.4
20	None	3130	37	Vaginal	3.1
21	None*	3945	38	Vaginal	2.8
22	None	2820	38	Vaginal	3.4
23	None	3005	38	Vaginal	2.4
24	None	2470	38	Vaginal	3.0
25	Contracted pelvis	2700	38	Section	2.9
26	None	3200	39	Vaginal	1.8
27	None	3540	39	Vaginal	1.6
28	None	3540	39	Vaginal	2.4
29	None	3095	39	Vaginal	2.8
30	None	3940	39	Vaginal	2.2
31	None	3075	39	Vaginal	2.8
32	None	2910	39	Vaginal	3.3
33	None	3150	39	Vaginal	2.6
34	None	2890	39	Vaginal	4.3
35	None	3530	39	Vaginal	2.8
36	None	3660	40	Vaginal	3.2
37	None	2950	40	Vaginal	3.0

TABLE I—*Continued*

NO.	MATERNAL DIAGNOSIS	BABY WEIGHT OR MEASUREMENT	DURATION OF PREGNANCY	TYPE OF DELIVERY	Q_{O_2}
		grams	*weeks*		
38	Chronic hypertension	4320	40	Vaginal	3.4
39	None	3400	40	Vaginal	2.7
40	None*	4000	40	Vaginal	3.4
41	None	4590	40	Vaginal	3.0
42	None	3400	40	Vaginal	3.4
43	None	3275	40	Vaginal	2.3
44	None	3420	40	Vaginal	1.7
45	None	3440	40	Vaginal	2.5
46	None	3165	40	Vaginal	2.2
47	None	3960	40	Vaginal	2.6
48	None	3400	40	Vaginal	3.1
49	None	3610	40	Vaginal	1.9
50	Rectal stricture	2665	40	Section	2.5
51	None	3870	40	Vaginal	2.3
52	Contracted pelvis	3925	40	Section	2.4
53	None*	2885	41	Vaginal	2.1
54	None	3660	41	Vaginal	1.6
55	None*	3280	41	Vaginal	2.2
56	None	3400	41	Vaginal	2.9
57	None	3030	41	Vaginal	1.8
58	None	3330	41	Vaginal	3.0
59	None	3960	41	Vaginal	1.9
60	None	3470	42	Vaginal	1.9
61	None	3020	42	Vaginal	1.3
62	None	3200	42	Vaginal	3.4
63	None*	3300	43	Vaginal	2.5

* Borderline blood pressure elevation either in labor or the puerperium. No albumin.

was absorbed by .2 of cc of 20 per cent potassium hydroxide in the central well. Atmosphere of room air was used. All observations were made in the Warburg apparatus at a constant temperature of 38 degrees centigrade. Readings were taken every 15 minutes for a period of 1 hour after equilibrium had been established. When the experiment was completed the tissue was washed with distilled water, dried overnight at 110 degrees centigrade and weighed. Oxygen consumption was expressed in cubic millimeters of oxygen per milligram of dry weight of placenta per hour.

In the study of the anaerobic metabolism of the placenta an entirely

different group of patients was used. In all 83 placentas were studied, 60 from normal patients, 5 from patients with chronic hypertensive disease, 15 from mothers having severe, acute toxemia and 3 from eclamptics. The placentas were handled in the same way as described above except that they were suspended in 2.7 cc of bicarbonate Ringer's solution at a pH of 7.4. In all instances again 2 mg. of glucose were added to each cc of bicarbonate Ringer's solution. The flasks were gassed with a mixture of 95 per cent nitrogen and 5 per cent carbon

TABLE II

Oxygen Consumption of the Placenta

(Severe Toxemia)

NO.	BABY WEIGHT OR MEASUREMENT	DURATION OF PREGNANCY	TYPE OF DELIVERY	Q_{O_2}
	grams	*weeks*		
1	800	28	Vaginal	2.4
2	1950	33	Vaginal	2.5
3	1550	34	Cesarean section	2.6
4*	1880	36	Vaginal	1.8
5	A. 2800	37	Vaginal	2.7
	B. 2745			
6	2580	37	Vaginal	2.8
7	3035	38	Vaginal	2.7
8	3120	39	Vaginal	2.8
9	3000	39	Vaginal	1.5
10	2690	39	Vaginal	2.6
11	3030	39	Cesarean section	3.2
12	3475	41	Vaginal	2.5
13	3305	42	Vaginal	3.0

* Eclampsia.

dioxide for 15 minutes. The readings were again taken every 15 minutes and after the experiment was finished the tissues were washed with distilled water and dried and weighed in the manner described above. The anaerobic glycolysis was expressed in cubic millimeters of carbon dioxide liberated per milligram of dry weight of placenta per hour.

In every instance a piece of placenta was prepared for microscopic examination in order that the morphological structure of the villi might be determined.

TABLE III

Anaerobic Glycolysis of the Placenta Control Series

NO.	MATERNAL DISEASE	BABY WEIGHT OR MEASUREMENT	DURATION OF PREGNANCY	TYPE OF DELIVERY	Q^{N}_{2}
		cm.	*weeks*		
1	Heart disease	C.R. 2.1	8	Hysterotomy	10.5
2	Nephritis	C.R. 1.0	8	Hysterotomy	10.5
3	Chronic hypertensive disease	C.R. 3.5	9	Hysterotomy	10.0
4	Tuberculosis	C.R. 5.0	11	Hysterotomy	10.0
5	Huntington's chorea	C.R. 6.0	12	Hysterotomy	5.9
6	Chronic hypertension	C.R. 4.0	12	Hysterotomy	9.2*
7	Tuberculosis	C.R. 6.5	12	Hysterotomy	10.2
8	Tuberculosis	C.R. 3.5	14	Hysterotomy	11.4
9	Chronic hypertension	Unknown	20	Hysterotomy	8.0*
10	Heart disease	C.R. 18.5	22	Hysterotomy	9.5
		grams			
11	None	950	27	Vaginal	7.6
12	None	980	28	Vaginal	4.7
13	None	1015	29	Vaginal	6.0
14	None	1537	31	Vaginal	4.8
15	Premature separation	1700	33	Cesarean section	8.8
16	None	2960	35	Vaginal	5.3
17	Placenta previa	2480	36	Cesarean section	6.15
18	None	2360	36	Vaginal	6.5
19	None	2200	36	Vaginal	9.9
20	None	2595	36	Vaginal	6.7
21	None	3130	37	Vaginal	6.5
22	None	2390	37	Vaginal	6.3
23	Contracted pelvis	2700	38	Cesarean section	7.1
24	None	2470	38	Vaginal	5.4
25	None	3005	38	Vaginal	5.0
26	Previous section	3950	38	Cesarean section	6.6
27	Contracted pelvis	2635	38	Vaginal	6.4
28	None	3000	38	Vaginal	5.4
29	None	3240	39	Vaginal	5.1
30	None	3150	39	Vaginal	5.8
31	None	3075	39	Vaginal	5.0
32	None	3940	39	Vaginal	4.6
33	None	3540	39	Vaginal	6.5
34	None	2910	39	Vaginal	5.4
35	None	3540	39	Vaginal	6.0
36	None	3095	39	Vaginal	5.0
37	None	3495	40	Vaginal	5.2
38	Tuberculosis	2750	40	Vaginal	5.5

TABLE III—*Continued*

NO.	MATERNAL DISEASE	BABY WEIGHT OR MEASUREMENT	DURATION OF PREGNANCY	TYPE OF DELIVERY	$Q_{O_2}^{N_2}$
		grams	*weeks*		
39	None	4000	40	Vaginal	6.6
40	Cystitis	4590	40	Vaginal	5.9
41	None	3400	40	Vaginal	5.6
42	None	3610	40	Vaginal	7.3
43	None	3660	40	Vaginal	5.5
44	None	3400	40	Vaginal	6.4
45	None	3500	40	Vaginal	6.5
46	None	3500	40	Vaginal	5.96*
47	None	3275	40	Vaginal	4.6
48	Rectal stricture	2665	40	Cesarean section	8.3
49	None	3870	40	Vaginal	8.1
50	None	3960	40	Vaginal	5.2
51	None	2780	40	Vaginal	7.12
52	None	3700	40	Vaginal	4.84
53	Heart disease	4165	40	Vaginal	4.88
54	None	4385	40	Vaginal	5.1
55	None	3245	40	Vaginal	6.9
56	None	3280	41	Vaginal	3.5
57	None	3400	41	Vaginal	6.2
58	None	3490	41	Vaginal	6.4
59	None	3250	41	Vaginal	6.3
60	Chronic hypertension	3600	41	Vaginal	7.3*
61	None	3020	42	Vaginal	4.33
62	None	3935	42	Vaginal	5.9
63	None	3800	42	Vaginal	5.75
64	None	3460	42	Vaginal	5.8

* Is same as other control series.

The oxygen consumption of the normal placenta and that associated with acute toxemia is shown in Figure 1 and Tables I and II. The general trend in oxygen consumption of the normal placenta confirms the previous studies done in this laboratory and the more recent work of Page (7). The values in the present study, however, are somewhat greater than those previously obtained here because of the addition of glucose to the substrate during the current series of observations. The Q_{O_2} decreases from 5 to 6 millimeters per milligram of placenta per hour in early pregnancy to approximately 3 cubic millimeters. If one superimposes upon this curve the results obtained in the cases of

TABLE IV

Anaerobic Glycolysis of the Placenta Severe Toxemia

NO.	BABY WEIGHT OR MEASUREMENT	DURATION OF PREGNANCY	TYPE OF DELIVERY	$Q_{N_2}^{CO_2}$
	grams	*weeks*		
1*	1000	29	Cesarean Section	6.4
2	1950	33	Vaginal	3.1
3	2000	34	Cesarean Section	6.8
4	1550	34	Cesarean Section	3.8
5*	1880	36	Vaginal	3.6
6	2300	37	Cesarean Section	6.8
7	A. 3025	37	Vaginal	6.4
	B. 2695			
8	3035	38	Vaginal	4.9
9	2685	38	Vaginal	7.3
10	3030	39	Cesarean Section	5.0
11	A. 2800	39	Vaginal	4.2
	B. 2745			
12	3170	40	Cesarean Section	6.4
13	2640	40	Vaginal	5.3
14*	3225	40	Vaginal	5.3
15	3000	41	Cesarean Section	7.7
16	3305	42	Vaginal	4.2

* Eclampsia.

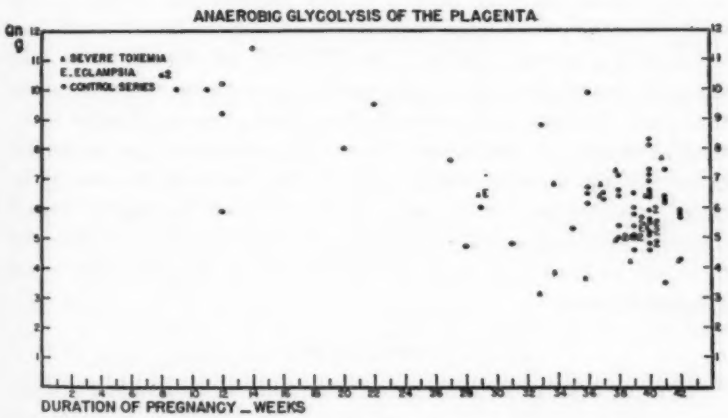

FIG. 2

acute toxemia it becomes apparent that there is no diminution in the oxygen uptake of the placenta in this latter group.

The lactic acid production of the normal human placenta also decreases as pregnancy progresses, falling from a high of 11 cubic millimeters of carbon dioxide produced per milligram of placenta per hour in early pregnancy to approximately 7 cubic millimeters. When one superimposes upon this curve the results obtained in the cases of acute toxemia it is apparent again that there is no consistent or significant decrease in the anaerobic glycolysis of the human placenta associated with this condition. These data are given in Tables III and IV and shown graphically in Figure 2.

DISCUSSION

The decrease in oxygen consumption and in the anaerobic glycolysis of the human placenta as pregnancy advances is consistent with the histological picture of aging in this organ. The disappearance of Langhan's layer, the increase in nuclear knotting and syncytial degeneration, should all lead to a decrease in metabolism of the villi. If then, the effect of chronic ischemia on the placenta is one of premature aging, the oxygen uptake or the anaerobic glycolysis, or both, should show an acute decrease in toxemia above and beyond that already shown by the normal placenta. Such a change has not been shown in this study. The fact that these placentas were normal histologically and behaved in a normal fashion in the Warburg machine as far as their anaerobic metabolism and oxygen uptake are concerned does not prove that these placentas were normally functioning organs. It must be remembered that no significant alteration in oxygen uptake or aerobic glycolysis was found in the kidneys of dogs with experimentally induced hypertension. On the other hand, the above findings of normal placental metabolism in the face of severe toxemia are not particularly favorable to the theory of placental ischemia as the etiological agent of acute toxemia.

CONCLUSION

1. A decrease in oxygen consumption and in anaerobic glycolysis was found in normal human placentas from the onset of pregnancy to term.

2. The oxygen consumption and anaerobic glycolysis were not significantly altered in cases of severe, acute toxemia including eclampsia.

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THE CORRELATION BETWEEN THE EAR THICKNESS AND SATURATION READINGS OF THE MILLIKAN OXIMETER[1]

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The Millikan oximeter (1, 2) is an instrument which measures the blood arterial oxygen saturation by the transmission of light through the intact human ear. The arterial saturation is indicated by the saturation reading, which varies directly with the amount of oxyhemoglobin in the ear. Before saturation readings can be taken on a given subject, maximal vasodilatation of the ear must be produced by the heat of the oximeter earpiece bulb so that the blood in the path of the light is "arterialized". This maximal vasodilatation is indicated when the ear thickness reading, which varies inversely with the total amount of hemoglobin(oxy- and reduced) and other pigments in the ear, has reached a stable value and no longer continues to fall. Once the ear thickness reading is stable, the saturation reading is set at some known or assumed value, e.g. "100%" with normal subjects breathing pure oxygen. Any subsequent change in the saturation reading then indicates a change in the arterial oxygen saturation of the blood and should behave *independently* of the ear thickness reading of the subject.

The recent report of Lindgren (3), however, that the arterial oxygen saturation, as measured by the Millikan oximeter, was higher in female subjects than in males and our knowledge that the ear thickness reading is also higher in females suggested to us that these two readings did *not* behave independently of one another and that the saturation reading might therefore be in some manner affected by the ear thickness reading.

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It is the purpose of this paper to report the observations made on a large group of normal subjects to demonstrate that the arterial oxygen saturation of the Millikan oximeter is *not* independent of the ear thickness reading.

Method. The arterial oxygen saturation readings on room air were obtained by allowing the subject to inhale oxygen, setting the saturation at "100" (1) and then turning back to room air. The same Millikan oximeter with one of two commercially available earpieces (4) was used for all tests. The subject was usually recumbent and allowed to rest approximately 30 minutes before inhaling the oxygen. At the

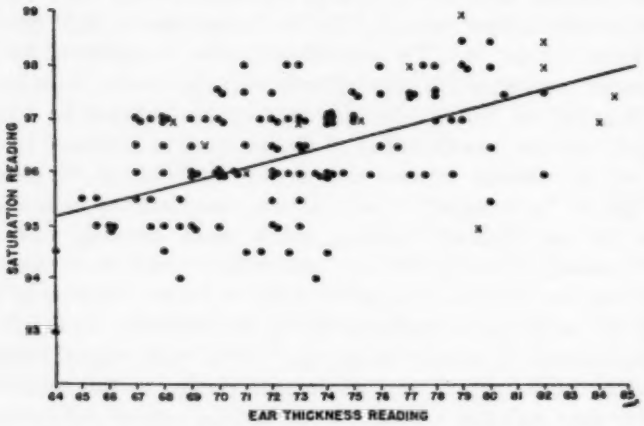

FIG. 1. The room air saturation versus the ear thickness reading
● indicates male subject. × indicates female subject.

beginning of this period, the earpiece, which had been previously "warmed up," was attached to the subject's ear and the ear thickness allowed to stabilize.

Observations. 134 room air saturation and ear thickness readings were obtained on 124 healthy white subjects, 12 of whom were females. The saturation and ear thickness for each subject are plotted in Figure 1. Statistical values for the entire group are presented in Table 1.

From inspection of the data in Figure 1 it is apparent that there exists a *direct* correlation between the ear thickness and room air saturation readings in our group of subjects; the greater the ear thickness, the greater the saturation. The distribution of these readings

also suggests that this relationship is a *linear* one. It is therefore possible to draw a straight line from these data from the formula $y = a + bx$ by substituting S_o for y and E_o for x, where S_o and E_o are the observed saturation and ear thickness, respectively, and a and b are constants. Such a line (fitted by the method of least squares, using vertical residuals) is shown in Figure 1. The "slope" of this line, b, equals .13 and is statistically very highly significant when compared to a slope of zero with "P" < 0.0002.

TABLE 1

The room air saturation and ear thickness readings for the entire group of observations

	NO.	MEAN	RANGE	ST. DEV.	ST. ERR. OF MEAN
Saturation	134	96.4	93–99	1.13	.10
Ear thickness	134	72.8	64–84.5	4.50	.39

TABLE 2

Comparison of room air saturation values in those subjects with the highest (H) and lowest (L) ear thickness readings

		NO.	MEAN	RANGE	ST. DEV.	ST. ERR. OF MEAN	"p"*
Male and female subjects	H	21	97.4	95–99	.96	.21	<0.0002
	L	22	95.8	93–97	1.12	.24	
Male subjects only	H	20	97.3	96–98.5	.81	.18	<0.0002
	L	21	95.7	93–97	1.08	.24	

* Indicates probability that differences between the two groups are due to chance. Values listed were obtained from those subjects in Figure 1 on whom only one observation was made.

This direct correlation between the ear thickness and saturation was found to be true regardless of the sex of the subjects studied. This is illustrated in Table 2, where two groups of subjects are compared—those with the highest ear thickness and those with the lowest ear thickness. The mean difference of the saturation between the two groups compared was just as great (1.6% units) and as satistically significant when the groups consisted of males alone as when female subjects were included.

Discussion. It has been demonstrated that the room air saturation of the Millikan oximeter varies directly with the ear thickness reading of the subject. If the saturation reading has behaved independently of the ear thickness reading then the data plotted in Figure 1 would have fallen around a *horizontal* line and there would have been no significant difference in the mean saturation values between those subjects with the highest ear thickness and those with the lowest.

This correlation between the ear thickness and saturation readings indicates that, in measuring the arterial oxygen saturation with the Millikan oximeter, some systematic error is being made as there is no apparent reason to believe that persons with relatively high ear thickness readings actually have a higher percentage of oxyhemoglobin in their arterial blood. The fact that such an error is being made has been suggested by Coleman who states "there is reason to believe that with extremely thick or very thin ears the indicated saturation may differ significantly from the true value" (4). This correlation between the ear thickness and saturation readings is in complete agreement with the observation that "the increase of saturation indicated by the Millikan oximeter when the subject breathes oxygen, following the breathing of air, is smaller in young, adult healthy white females than in young, adult healthy white males" (5).

The data accumulated on our group of 124 normal subjects do not allow us to draw any conclusions as to the nature of the technical feature of the oximeter responsible for this relationship between the saturation and ear thickness readings. They do, however, allow us to make some type of *empirical* correction of the observed saturation of a given subject for his particular ear thickness reading. This can be done if one is willing to assume that the true saturation is the same as the observed saturation when the subject's ear thickness reading happens to fall on the mean ear thickness value for the entire group. This mean value will naturally depend on the number and type of subjects constituting the group and possibly also on the particular Millikan oximeter being used. Such a corrected saturation reading may be obtained by the following formula

$$S = b(E_m - E_o) + S_o$$

where

S = corrected saturation

E_m = mean ear thickness of entire group of subjects = 72.8, and E_o, S_o and b are as previously described.

Thus the corrected saturation of a subject with an observed saturation of *95* and an observed ear thickness reading of *80* would be

$$.13(72.8 - 80) + 95 \text{ or } 94.1.$$

Similarly, the corrected reading of another subject with the same observed saturation but with an ear thickness of *66* would be *95.9*. This difference in the saturation reading of almost 2 scale units would be of considerable clinical importance if one were using the oximeter to detect the presence of an abnormal unsaturation of the arterial blood.

If it is found by other investigators using the Millikan oximeter that similar corrections for the ear thickness reading can be made for the observed saturations with hypoxemic subjects, as well as for normal subjects breathing room air, the overall accuracy and usefulness of the Millikan oximeter should be considerably enhanced.

Summary. From observations made on 124 normal subjects, it has been shown that there is a direct correlation between the ear thickness reading and the arterial oxygen saturation reading of the Millikan oximeter and that these two readings, therefore, do *not* behave independently of one another. Because of this relationship it is believed that the saturation, when measured by the oximeter, may be higher, or lower, than the subject's true saturation depending on whether his ear thickness reading is higher or lower than the average. A formula is presented whereby it is possible to obtain a corrected saturation according to the subject's ear thickness reading.

I should like to express my appreciation to Dr. Rowland V. Rider for his advice in the statistical analysis of the data and to Miss Grace Saltzer for technical assistance.

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THE EFFECTS OF POSTERIOR PITUITARY EXTRACT AND SMOKING ON WATER, SODIUM AND CHLORIDE EXCRETION IN NORMAL SUBJECTS AND IN PATIENTS WITH CONGESTIVE CARDIAC FAILURE

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I. INTRODUCTION

The sequence of physiological events leading to the accumulation of extracellular fluid in patients with congestive cardiac failure is still uncertain (1–10). Experimental evidence has shown the presence, in this form of cardiac failure, of a marked derangement of renal circulation (11, 12, 13) and a decreased ability by the kidney to excrete water and sodium ions (14, 15, 16). Reports that antidiuretic substances can be recovered from the urine of patients suffering from edema of various causes (17, 18, 19, 20) have suggested the possibility that the action of the antidiuretic hormone of the posterior pituitary gland may be of etiological significance in the renal retention of water in congestive cardiac failure.

It has been reported previously that mild muscular exercise in both normal and edematous cardiac patients causes an antidiuresis in association with a sodium retaining response (21, 22). Furthermore, speculation has been made as to the significance which this response may have in the progressive accumulation of water and sodium ions by ambulant patients, prior to cardiac decompensation. This antidiuresis of exercise has been attributed to posterior pituitary antidiuretic action on the renal excretion of water (23, 24). Therefore, it seemed necessary to ascertain whether the acute administration of posterior pituitary preparations would influence the excretion of urinary sodium and chloride in a manner similar to that seen during muscular exercise.

Reports that nicotine or smoking inhibits a water induced diuresis by stimulation of the supra optic hypophyseal tract (25, 26) suggested

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that this method could be used in producing an antidiuresis for the purpose of the present investigation. This paper will report the effects on glomerular filtration rate, the urinary excretion of sodium chloride and water of (1) the intravenous administration of pitressin in normal controls and in 3 patients with congestive cardiac failure, (2) the effect of smoking in normal subjects.

II. EXPERIMENTAL PROCEDURE AND METHODS

1. *Clinical Material*

The normal subjects used were adult males who were in good health. The patients who were suffering from congestive cardiac failure were taken either from the wards of the Medical Service of the Johns Hopkins Hospital or from the Out Patient Cardiac Clinic. All had had previous episodes of cardiac decompensation and had not received any mercurial diuretics for a period of one week prior to the test procedure being carried out.

Case No. 1, (L. S.) #441984, C. F. Age: 40. First admission to the Johns Hopkins Hospital on 11-4-47 with history characteristic of cardiac decompensation resulting from chronic rheumatic endocarditis. Mitral stenosis and aortic insufficiency were present. Patient followed in the Out Patient Cardiac Clinic from January, 1948 until August, 1949, during which period she was treated for one episode of cardiac decompensation. At the time of the present study, exertional dyspnea existed. Significant findings were blood pressure 135 mms. Hg systolic, 60 mms. Hg diastolic. Pulse showed auricular fibrillation. The heart was enlarged, the PMI being 13 cms. to the left of the midline in the sixth intercostal space. An aortic diastolic murmur to the left of the sternum and mitral systolic and diastolic murmurs were heard. Slight ankle edema was present, with elevated jugular venous pressure and mild hepatomegaly.

Case No. 2, (W. C.) #209680, W. M., Age: 60. First admission to the Johns Hopkins Hospital on 5-18-49 with history of four months exertional dyspnoea, orthopnoea, and ankle edema. The patient was then treated with digitalis and mercurial diuretics for congestive cardiac failure resulting from arteriosclerotic heart disease with auricular fibrillation. He was subsequently followed in the Out Patient Cardiac Clinic until August, 1949, when the following physical findings were present. Weight 147 lbs., B.P. 128 mms. Hg systolic, 72 mms. Hg diastolic. Pulse showed auricular fibrillation. The heart was slightly enlarged and a mitral systolic murmur of innocent quality was heard. The lower margin of the liver was just palpable, the veins in the neck were engorged to the angle of the mandible and pitting edema of the ankles was present.

Case No. 3, (E. A.) #51116, C. M., Age: 55. First admission to the Medical Service Johns Hopkins Hospital 8-19-49 with three months history of increasing shortness of breath or exertion and orthopnoea. Six weeks prior to admission, patient noticed for the first time, swelling of ankles which did not disappear over-

night. Significant physical findings at time of admission were B.P. 130 mms. Hg systolic, 80 mms. Hg diastolic. Pulse was irregular in time, the electrocardiograph showing frequent auricular and ventricular extrasystoles. Radial arteries were thickened and tortuous. The heart was enlarged with the PMI in sixth left intercostal space. No murmurs were heard. The jugular venous pressure was raised, a small effusion was present in the right pleural cavity, the liver was enlarged two inches below the right costal margin and pitting edema was present at the ankles. NPN 33 mgm.% on admission. Urine showed a trace of albumin, and haematocrit and blood count were within normal limits.

2. *Experimental Procedure*

The experimental procedure allowed for sufficient water intake from the time of awaking in the morning until the test was performed in order to establish a urine flow of approximately 5–10 cc/min. Thereafter, 200 cc. of water were given following each urine collection period, the time of which was approximately fifteen minutes. After three to four control collection periods had been taken the test procedure was carried out. This consisted of either the intravenous administration of 0.1–0.04 units of Pitressin (Parke Davis and Company) in 10 cc. of 5% glucose or the smoking of two cigarettes. The time taken for either of these was 5–7 minutes. Urine collections were then continued at periods of 15–20 minutes until the urine flow had returned to control levels or if this did not occur for an average of four to six periods. Blood samples were taken as near as possible to the mid collection point for the determination of serum sodium and chloride levels.

3. *Methods*

The methods used in these experiments have been previously described (21, 22). Filtration rate was determined either by the inulin or endogenous creatinine clearance methods, and when inulin was used creatinine clearance was determined for comparison. Electrolyte excretion has beeen expressed as electrolyte clearance ratios, which are used to represent the changes in electrolyte excretion in terms of the relationship between the amount of electrolyte filtered through the glomeruli and the amount reabsorbed by the tubules. The expression clearance ration used in this paper means the percentage of filtered electrolytes *not* reabsorbed by the renal tubules. This expression is $\frac{\text{C (electrolyte)}}{\text{C (Inulin) or C (Creatinine)}} .100.$

III. RESULTS

1. *Glomerular Filtration Rate*

Chart 1 shows the changes in glomerular filtration rate which were observed during these experiments. In normal subjects in only one instance did a significant depression occur (S-S 2-18-49 132-115 cc/min). The remaining results are in accord with previous reports that small

doses of posterior pituitary extracts do not alter the rate of glomerular filtration (27). In two cardiac patients, a depression was observed, but the significance of this change cannot be judged. No change in sytemic blood pressure or pulse rate was recorded and the possibility of intrarenal redistribution of blood flow can only be cause for speculation (28).

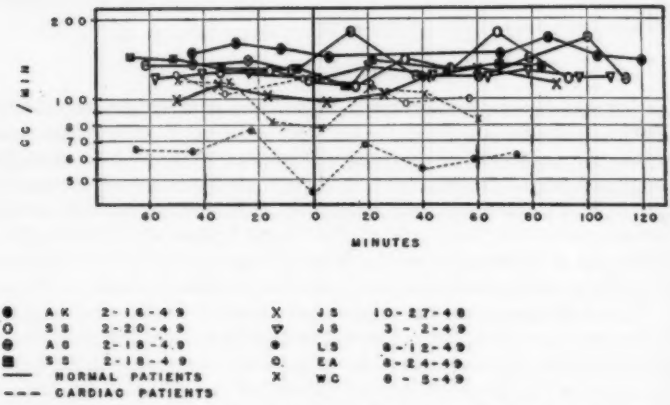

CHART 1. The effect on glomerular filtration rate (cc/min) of the intravenous administration of pitressin or of smoking. In this and subsequent charts, time is plotted as the abscissa. From the beginning until zero time is the control period. The injection of pitressin or smoking were carried out one or two minutes before t = o.

The same symbols for each patient will be used in subsequent charts. The experiments (S.S. 2/20/49) (J.S. 3/2/49) (A.G. 2/18/49) were performed using nicotine as the posterior pituitary stimulant. Filtration rate in cardiac patients determined by inulin clearance method.

2. *Urine Flow*

As shown in Chart 2, a consistent antidiuresis occurred in all instances, the maximum depression of the ratio $\frac{UF}{CCr}$ occurring in the majority of cases within fifty minutes. This corresponds in time relationship to the decrease in urine flow observed during mild exercise (28). The magnitude of the change in urine flow or $\frac{UF}{CCr}$ in the present experiments is variable as both the initial urine flow varied and different

doses of pitressin were used in each instance. The dosage of pitressin was influenced by prior testing of the reaction of the subjects to the preparation in order to avoid untoward side effects. A difference between normal and cardiac subjects is seen in the duration of the antidiuresis—in the latter instance, this persisted until the end of the experimental procedure.

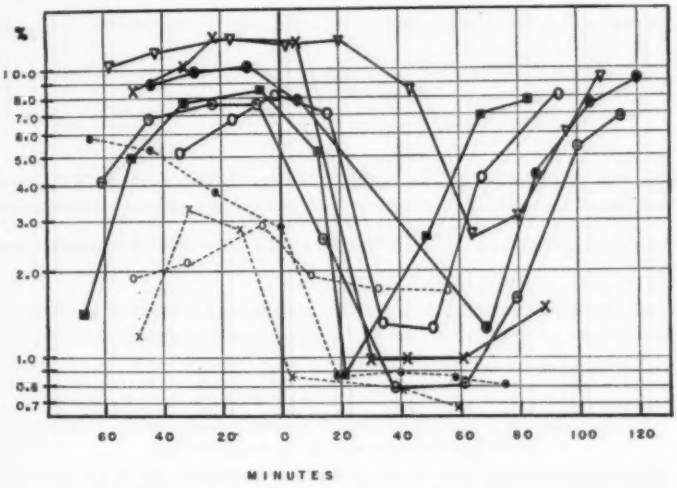

CHART 2. The effect on urine flow of the intravenous administration of pitressin or of smoking. Test procedure carried out at t = o. Ordinate shows logarithmic scale for the ration $\frac{UF}{C_{ur}} \times 100$, which is the percent of the water filtered by the glomeruli which is excreted in the urine. The symbols used are identical to those in Chart 1.

3. *Sodium Excretion*

Sodium clearance ratios are shown in Chart 3 and it will be seen that no significant change followed the test procedure in spite of the marked reduction in urine flow. This finding is in contrast to that observed during mild muscular exercise in which a consistent reduction in sodium excretion occurs at the time of the antidiuresis of exercise. The alterations in urinary concentration and rate of excretion of sodium during two typical experiments of the present series are seen in Table 1. The effect of posterior pituitary action is seen to be exclu-

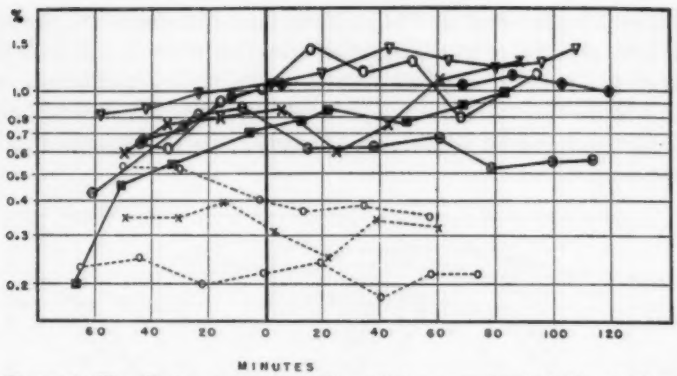

CHART 3. The effect on sodium excretion of intravenously administered pitressin or smoking at t = o. Time in minutes is plotted as the abcissa, ordinate shows logarithmic scale for ratio $\frac{C_{Na}}{C_{cr}} \times 100$, which is the per cent of the sodium filtered by the glomeruli which is excreted in the urine.

There is a general tendency for sodium excretion to rise during the control period (before t = o) probably due to the rising urine flow (see Chart 2).

TABLE 1

This table shows the changes in the concentration and rate of excretion of sodium in two experiments on normal subjects in Chart 3.

The increase in sodium excretion in the first three collection periods is observed during the time in which an adequate diuresis is established.

The experimental procedure was carried out immediately after the third collection period.

	EXPERIMENT					
	A. K. 2-16-49 (I.V. Pitressin)			J. S. 3-2-49 (Smoking)		
Collection Period	Conc. Na Meq/L	UV Na Meq/min	$\frac{CNa}{CCr} \times 100\%$	Conc. Na Meq/L	UV Na Meq/min	$\frac{CNa}{CCr} \times 100\%$
U 1	11.2	.183	.76	10.6	.159	.87
U 2	13.5	.220	.96	11.2	.184	.99
U 3	19.7	.225	1.1	12.5	.191	1.1
U 4	124.0	.230	1.1	14.3	.234	1.2
U 5	39.0	.284	1.2	24.5	.255	1.5
U 6	20.3	.26	1.1	70.0	.227	1.3
U 7	15.8	.206	1.0	56.0	.238	1.3

sively on the reabsorption of water as the rate of excretion of sodium (mg/min) remains unaltered.

4. *Chloride Excretion*

Chloride excretion is shown in Chart 4 from which it is seen that the excretion ratios closely follow those for sodium excretion (Chart 3). The rate of chloride excretion during a posterior pituitary antidi-

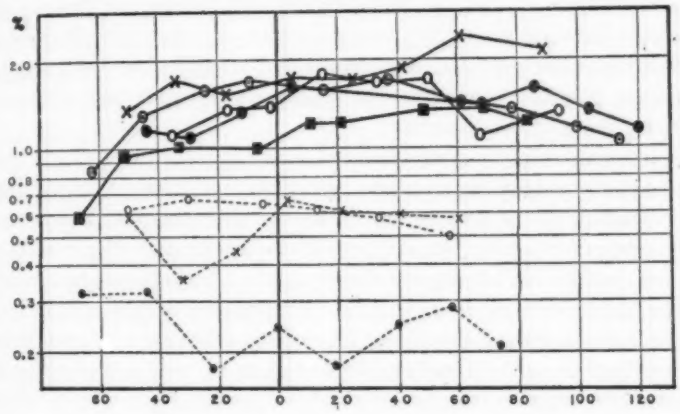

CHART 4. Chloride excretion as determined in the present investigation. Ordinate shows logarithmic scale for ratio $\frac{C_{Cl}}{C_{Cr}} \times 100$ which is the per cent of chloride filtered by the glomeruli which is excreted in the urine. Symbols are identical to those used in Chart 1. Pitressin given or smoking at t = o.

uresis although generally accepted as being increased (29, 30, 31) is subject to some variations (32, 33). The results of these experiments do not support the suggestion that "the secretion of the posterior gland hormone has an inhibitory effect upon the tubular reabsorption of chloride" (33).

DISCUSSION

In normal subjects the inhibition of a water induced diuresis by the action of intravenously administered posterior pituitary extracts or of

smoking is due to the increased tubular reabsorption of water. A similar inhibition of urine flow provoked by exercise is also well known. Klisiecki, Pickford, Rothschild, and Verney (34) have shown that the similarity of the time course of such an inhibition is comparable to that following the injection of posterior lobe extracts and they suggest that the antidiuretic hormone is responsible for the response observed during exercise. A decrease in glomerular filtration can occur during severe exercise (35, 36, 37) contributing also to the antidiuretic response—but mild grades of exertion produce no change in the rate of glomerular filtration (21). It seems likely therefore that the posterior pituitary gland is responsible for the decrease in urine flow which occurs during muscular exercise.

In exercise causing an antidiuretic response, both the rate of excretion and the urinary concentration of sodium and chloride are reduced. Our results show that reductions in sodium and chloride excretion are not observed following the intravenous administration of pitressin or of smoking. Before attributing the changes in electrolyte excretion observed during exercise to an increase in tubular reabsorption of sodium and chloride from the glomerular filtrate, consideration has been given as to whether such alterations might not arise from a depression in glomerular filtration rate, undetectable by present day methods of determination.

Evidence contrary to such a belief is seen in (I) the decrease in concentration of urinary sodium during exercise, indication that the reabsorption of sodium in relation to water has increased, (II) the sodium retention due to exercise has been observed with a perceptible increase in glomerular filtration rate, (III) the dissociation of the behaviour of the ratio $\frac{UF}{CCr}$ from the ratio $\frac{CNa}{CCr}$ seen in the present experiments which indicates no correlation with the rate of filtration. It is felt, therefore, that apart from the osmotic relationships dictating reabsorption within the lumen of the renal tubules, there exist independent mechanisms both for the control of water and sodium excretion which are responsible for the final electrolyte composition of the urine. In a recent review on the mechanism of excretion of strong electrolytes, Homer Smith has stated "that it is believed that the reabsorption of sodium by the renal tubules is operationally independent of the reabsorption of water." (38).

Walker et al (39) by direct analysis of mammalian tubular fluid have shown that approximately 80% of the water of the glomerular filtrate is absorbed within the proximal tubular segment leaving the remainder to be passed on to the loop of Henle and the distal segment for the process of 'facultative reabsorption' (40). The limiting factor which appears to control this distal reabsorption is the osmotic pressure of the urine conditioned finally by the concentration of urea and sodium salts (41). Shannon has stressed the importance of a "glomerular-tubular balance" in electrolyte excretion; this being of importance "if the reabsorption of an osmotically active material in the proximal portion of the nephron indirectly provides the force for the reabsorption of a large portion of filtered water" (31). His experiments carried out on dogs with diabetes insipidus were performed in an attempt to elucidate this relationship between the individual processes of proximal and distal reabsorption within the nephron. He concluded that the two characteristic actions of the hormone of the posterior pituitary gland were the facilitation of the active renal tubular reabsorption of water distally and the inhibition of tubular reabsorption of sodium in the proximal segment of the nephron. From the data on humans reported in this paper, no evidence could be found that the excretion of sodium had been increased significantly following the administration of pitressin.

The effect of the intravenous administration of pitressin in patients with congestive cardiac failure, although observed on only three cases, appears to be similar to that obtained in normal subjects. Although a wider range in the determination of the ratio $\frac{CNa}{UF}$ is seen in Chart 3, no striking increase or decrease of sodium excretion is seen following the test injection. Its mode of action would seem, therefore, to be similar to that in normal subjects.

Peters (42) in reviewing the role of sodium reabsorption in the formation of edema has stated that "the most powerful known stimulus to the reabsorption of sodium appears to be the need to conserve water." If such a statement represents the teleological necessities of tubular reabsorption in respect to water and sodium excretion one is forced to speculate (1) why, in congestive cardiac failure does the kidney continue to conserve water when the fluid compartments of the body already contain an excess of isotonic salt solution and (2) that two distinct mechanisms, apart from the normal tubular osmotic influences,

are responsible for the reabsorption of sodium and water since posterior pituitary extract has been shown to exert its influence exclusively on the reabsorption of water. In relation to (1) Peters has suggested that some function possibly related to the volume of circulating plasma may supply the stimulus which is responsible for the continual and abnormal retention of water—the nature of which is yet unknown. In answer to (2) deductions from the evidence of Walker and others that sodium salts have a topographical priority over water in the process of reabsorption (42) suggest that the renal defect (possibly of adrenal origin) in edema formation of congestive cardiac failure may rest in the abnormal reabsorption of sodium in the proximal tubule, thus permitting the reabsorption of water to occur more extensively against a lessened osmotic gradient in the distal portion of the nephron. This is suggested from the evidence obtained from the present study. In cases of congestive cardiac failure a low sodium clearance is associated with a more prolonged antidiuresis following the same dose of pitressin which was administered to normal subjects.

The influence which the adrenal cortex exerts over the level of sodium and chloride in the serum has been known since the reports of Bauman (43), and the dramatic results attendant upon replacement therapy in patients with Addison's disease (44, 45) has lead to a fuller comprehension of the mechanism of water and electrolyte control as influenced by the adrenal cortex. However, there has accumulated, mainly through the work of Corey, Britton and Silvette, considerable evidence that an antagonism exists between the effects of adrenal cortical and posterior pituitary action on the renal excretion of sodium and water. This subject has recently been reviewed by Gaunt (46) who postulates that the mode of action of many of the adrenal cortical hormones on water metabolism is to enhance urine volume in two ways, (1) to augment thirst due to sodium retention, (2) to inhibit the tubular reabsorption of water. This hypothesis has its foundation on such facts as the inability to provoke a water induced diuresis in patients with Addison's disease, the establishment of a polyuria following the prolonged administration of desoxycorticosterone acetate (DOCA), the demonstration of increased circulating antidiuretic substances in the serum after adrenalectomy and the protective action of adrenal cortical compounds against experimentally produced water intoxica-

tion. Contrasting these adrenocortical effects with what he believes to be a physiological antagonism of the posterior pituitary gland, Gaunt states that there is abundant evidence that pitressin, in addition to its well known effect of increasing water reabsorption, enhances the excretion of sodium chloride.

From the results which have been presented in this study, no convincing evidence could be found that the sodium or chloride excretion was increased following the administration of pitressin, the mode of action of the latter preparation being "to check the excretion of water without altering the rate of elimination of sodium and chloride" (47). Peters (47), in reviewing much of the evidence upon which the concept of adrenal-posterior pituitary antagonism has arisen, has written that "if it be assumed that the action of DOCA on the kidney is identical with that of the natural cortical hormone, all phenomena that have been described, could be explained on the hypothesis that the adrenal cortical hormone promotes reabsorption of sodium while the posterior pituitary hormone promotes reabsorption of water. It is not necessary to suppose that the actions of these two hormones are antithetical." As far as this statement applies to the mode of action of the posterior pituitary gland, the results of this present investigation are in complete accord.

SUMMARY

1. Posterior pituitary action as judged from the intravenous administration of pitressin or from smoking causes no changes in glomerular filtration rate in normal subjects.

2. The antidiuresis due to posterior pituitary extract or smoking is not associated with any change in the rate of sodium or chloride excretion.

3. A similar response was observed when small doses of pitressin were given to patients suffering from congestive cardiac failure.

4. Electrolyte excretions occuring during the antidiuretic responses to exercise (walking) and to the intravenous administration of pitressin are dissimilar. Reduction in sodium and chloride excretion occurs without perceptible changes in glomerular filtration rate during mild exercise.

5. The dissimilar effects of exercise and pitressin on sodium and

chloride excretion are interpreted as being due to different physiological mechanisms, although the reduction in urine flow occuring during exercise is most probably due to posterior pituitary action.

6. It is unlikely that the accumulation of edema fluid in congestive cardiac failure is caused by posterior pituitary action on the kidney, since sodium chloride retention does not occur with the administration of small doses of pitressin.

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A METHOD FOR RECORDING BALLISTOCARDIOGRAPHIC VECTORS:

Preliminary Report

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Introduction: Heretofore, the ballistocardiograph has been used largely to record only those body vibrations which are directed parallel to the long axis of the body, yielding what may properly be termed head-foot (H-F) records. These records are obtained by designing the ballistocardiograph so that the bed on which the subject reclines is free to move only in the head-foot direction, being restrained to reduce motions in other directions (1). The pick-up device is so placed that it records only in the direction of freedom of motion. Variants of this method of head-foot recording include those designed for the sitting or standing subject, i.e., the vertical ballistocardiograph (2, 3).

It is apparent that the body motions resulting from transmitted cardiovascular forces are not restricted to the head-foot direction alone but must occur in other directions as well. If these body motions were recorded along the three body axes (head-foot, side-to-side and anterior-posterior) a complete vectorial representation could be made of them. While it is true that in the normal individual the magnitude of the body motions in the head-foot direction is greater than in the other two, it does not follow that these latter are negligible, nor does it follow that these same conditions apply when the ballistocardiographic form is abnormal. This field of the vector representation of ballistocardiographic deflections has not yet been explored.

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Starr and Friedland (4), in studies relating to the causes of the respiratory variation in amplitude of ballistocardiographic deflections, were convinced that this variation was not a result of the changes in the anatomical position of the heart. They reasoned that if the complexes become smaller during expiration because the long axis of the heart shifts farther away from the head-foot axis, then it should be possible to reverse the phase of the respiratory variation by turning the subject on the ballistocardiograph bed so that the long axis of the heart during expiration would be parallel to the head-foot axis of the bed. This experiment was carried out and the usual small complexes continued to appear during expiration. This is the only report in the literature dealing with an attempt to alter the phase or magnitude of ballistocardiographic complexes by turning the subject on the bed.

Hamilton and his co-workers (5) in 1945 published a diagram drawn from tracings made with a "three-directional ballistocardiograph"; the three curves represented deflections recorded in the head-foot, lateral and anterior-posterior directions. No indication was given as to the technical method by which these tracings were made but it was mentioned that three different recording systems were used simultaneously.

Braunstein and McGuire (6) are now engaged in studies dealing with the recording of simultaneous head-foot and lateral records.

It seemed desirable to explore the distribution of ballistocardiographic vectors in space for several reasons. Vector study of normal individuals might afford more and different information regarding the effect of such factors as body habitus, anatomical position of the heart and aorta, and respiration on the ballistocardiogram. It might shed new light on the physiological events giving rise to the ballistic deflections. Finally, a study of the vector patterns of subjects with abnormal ballistic forms might lead to a clearer understanding of the nature of the changes in circulatory mechanics occurring in these individuals.

A simple method has been devised for recording the ballistic complexes in all three directions (H-F, Lat. and A-P) and a description of this method is the purpose of the present paper.

Method: The method employs a modification of the conventional head-foot, high-frequency ballistocardiograph. A light wooden turntable similar in shape and

size to the moving platform of the ballistocardiograph bed is placed on its flat upper surface. A bolt through the center of both turntable and bed serves as a pivot about which the turntable can be rotated with respect to the ballistocardiograph bed. The turntable is equipped with a footboard and two vertical padded wooden supports which are adjacent to the left shoulder and left hip of a subject lying lengthwise on it. A simple method for clamping the turntable to the bed at any angle completes the construction.

This modification, then, permits rotation through 360° with respect to the long axis of the ballistocardiograph bed. The subject is placed flat on his back on the turntable with his feet firmly pressed against the footboard and with his left shoulder and left hip placed firmly against the side supports. The turntable is rotated manually to any angle in the frontal plane, clamped in place and a record is taken in the usual manner.

The convention used to describe the various rotations is simple. See Fig. 1. The two sides of the turntable are designated "rt." and "lt." to correspond to the subject's right and left sides as he lies flat on his back. When the long axis of the turntable lies in the long axis of the ballistocardiograph bed, this position is designated "0°" and yields the usual head-foot (H-F) record. When the turntable is rotated so that its *left* side is nearer the foot of the ballistocardiograph bed (clockwise rotation viewed from above), all angles within this semi-circle are termed "lt."; when the turntable is rotated so that its *right* side is nearer the foot (counterclockwise rotation), all angles within this semi-circle are termed "rt.". Thus if the turntable is rotated clockwise 30°, this position is designated "30° lt.". Positions "180° lt." and "180° rt." are identical, wherein the subject's head is at the "foot-end" of the ballistocardiograph bed and his feet are at the "head-end". The record made in this position is identical to the usual H-F record but is upside down. Records at "90° rt." or "90° lt." are lateral records (Lat.), one being the inverse of the other.

Routine records in the *frontal* plane are taken at "0°" (H-F), "60° lt.", "60° rt.", and "90° rt." (Lat.); more positions may be used if desired.

In order to record movements in the A-P direction, the turntable is rotated to the "90° rt." position; the subject is placed on his right side with the lower (hip) support against the sacrum and the upper (shoulder) support against the upper thoracic spine. The feet are pressed firmly against the footboard. In this position the anterior aspect of the body faces the "foot-end" of the bed while the posterior aspect of the body faces the "head-end" of the bed. Therefore, in this A-P position an anterior motion produces a negative (downward) deflection on the record while a posterior motion produces a positive (upward) deflection. A doubled pillow is placed under the head.

The use of this turntable, then, permits the recording of movements in the head-foot, lateral and anterior-posterior directions and supplies the data needed for vectorial representation of ballistic movements. These records cannot be taken simultaneously, which invalidates any claim to a high degree of fidelity for the derived vector loops; however, if respiration be suspended at approximately the same point in the respiratory cycle in each position, the consistent complexes

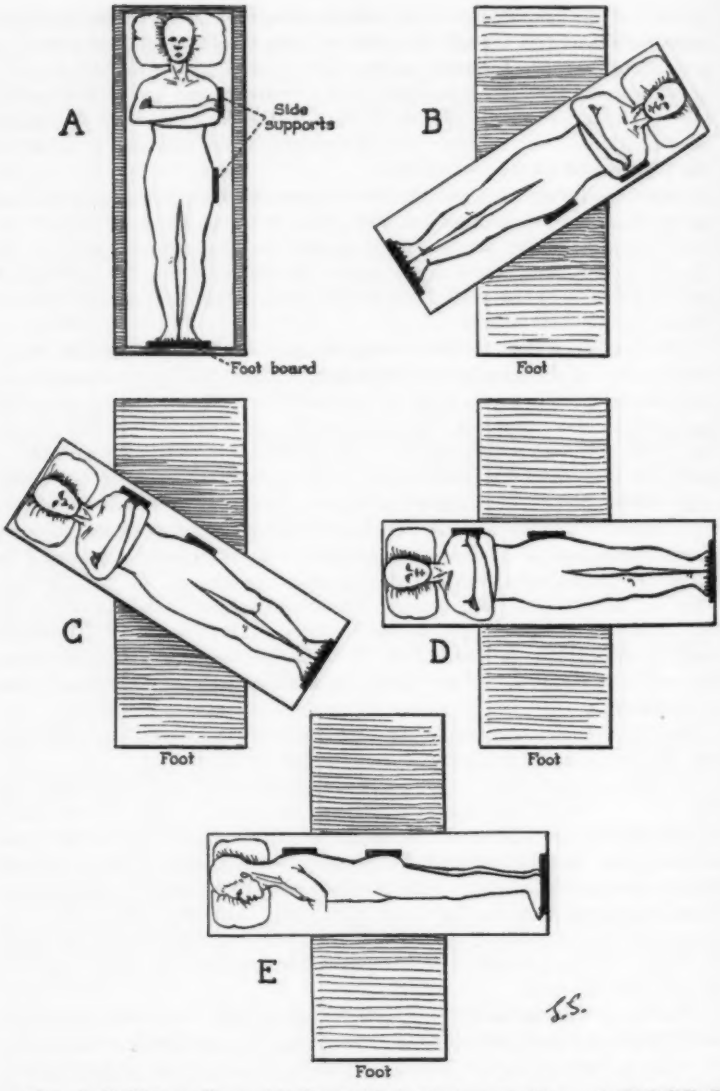

FIG. 1. Ballistocardiographic Turntable in Various Positions; A. H-F (0°), B. 60° lt., C. 60° rt., D. Lat. (90° rt.), E. A-P

which appear in each of the records may be used to make a rough approximation of the vector loops. A simultaneously recorded electrocardiogram on each of the three records supplies a cardiac time reference.

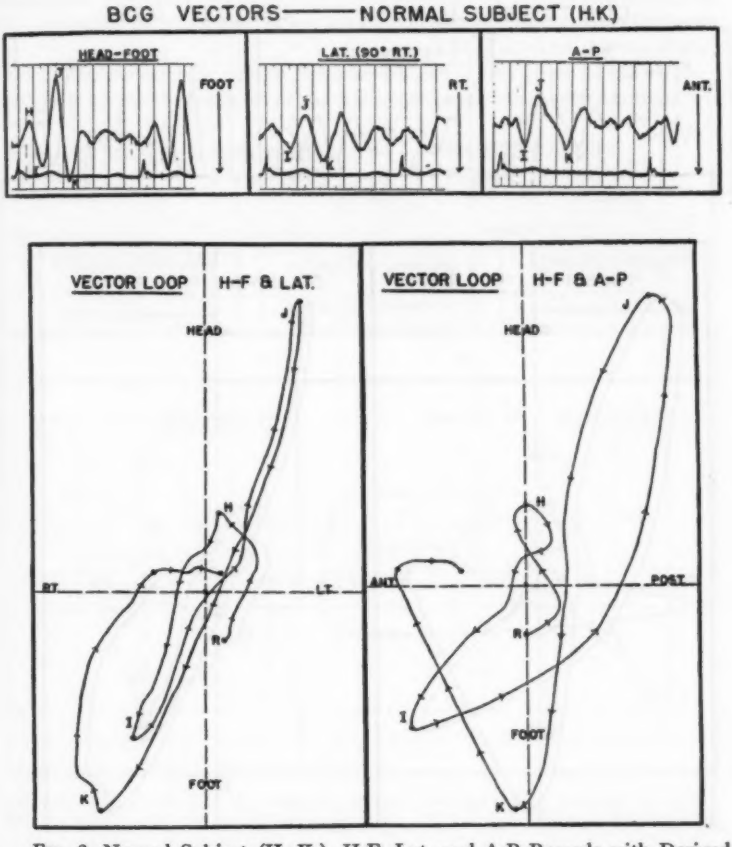

FIG. 2. Normal Subject (H. K.). H-F, Lat. and A-P Records with Derived Vector Loops. See text.

Calibration on all of these "three directional" records is the same. Occasionally a greater amplification and camera speed are used in order to make measurements easier (Fig. 2). In deriving the vector loops, baselines are drawn in on each of the three records and amplitudes are measured every 0.01 sec. starting with the peak of the R wave in the electrocardiogram and extending through about 0.4 sec.

These figures are then plotted on the two graphs and represent projections of the vector loops onto the frontal plane (H-F and Lat.) and onto the sagittal plane (H-F and A-P). The H-F amplitudes are plotted on the ordinates and the Lat. and A-P amplitudes on the abscissae. The vector loops for the different individuals presented herein are comparable in form but not in magnitude, for the graph scale factors are not the same in all cases.

It should be noted that in the H-F and A-P records, which are used to derive the sagittal loops, the position of the heart with respect to the body is not the

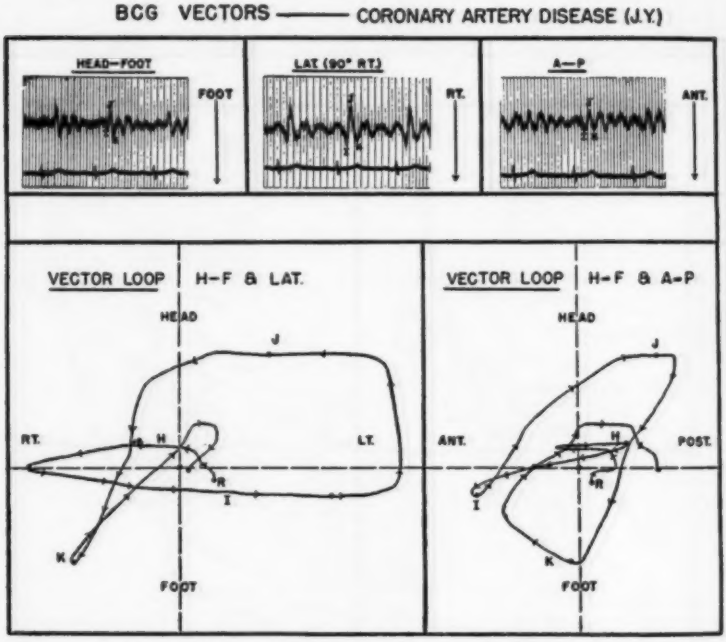

FIG. 3. Subject with Coronary Artery Disease (J. Y.). H-F, Lat. and A-P Records with Derived Vector Loops. See text.

same, for in the H-F record the subject is supine and in the A-P record he is on his right side. This undoubtedly results in some error but its magnitude will remain difficult to ascertain until a method for triaxial simultaneous recording is devised.

Results: Preliminary work indicates that consistent, reproducible records of good quality and amplitude can be obtained using the ballistocardiographic turntable described above. Fig. 2 shows the H-F,

Lat. and A-P records and the derived vector loops in a normal subject (H K.). These are characteristic of the majority of the approximately 45 normal individuals studied. In most cases the axis of the I wave is footward, slightly to the right and anterior, the J axis is headward, slightly to the left and posterior, and the K axis is footward and slightly to the right. No record on a normal subject has been

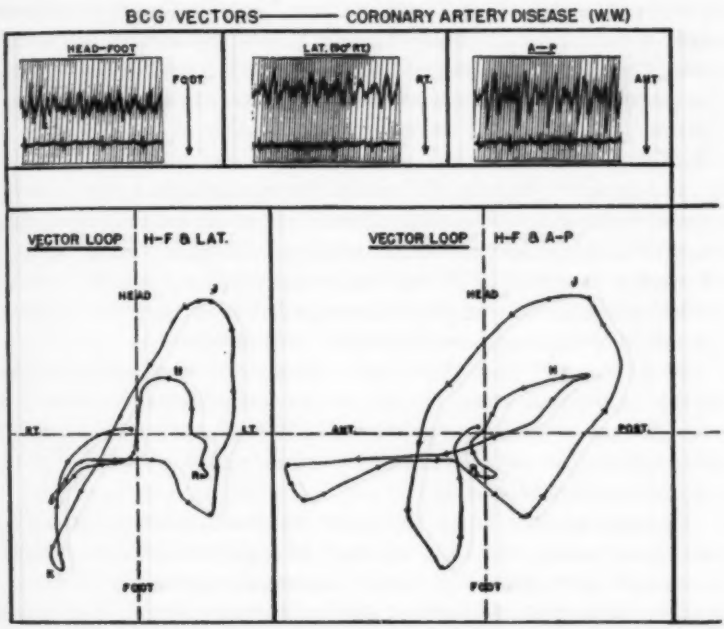

FIG. 4. Subject with Coronary Artery Disease (W. W.). H-F, Lat. and A-P Records with Derived Vector Loops. See text.

seen in which the deflections in the Lat. and A-P records were as large as those in the H-F.

In contrast to the graphs of normal individuals, subjects with cardiovascular disease often show marked alterations in their vector diagrams. The axes of the various waves may be quite different from those seen in normal subjects or the vector loops may be greatly distorted. It is not unusual to see records in which the Lat. or A-P deflections are larger than the H-F. In Figs. 3 & 4 are shown records

and the corresponding vector diagrams from two patients with coronary artery disease both of whom have hearts which are normal in size, shape and position.

In Fig. 3 (J. Y.) it is seen that the initial recoil resulting from ventricular systole (the I wave) results in a loop whose first portion is directed straight laterally to the right and anteriorly but whose final portion is to the left and anterior. The J loop has an indeterminate axis, is quite low and broad while the K loop and axis are fairly normal. The reason for the peculiar configuration of the I and J loops becomes readily apparent when one glances at the three tracings shown, for the I and J waves are much smaller in the H-F than in the Lat. record.

In Fig. 4 (W. W.) the H-F record shows a doubled I wave. In the vector loops it is seen that the "first" I wave is a strong movement footward, to the right and almost straight anterior, while the "second" I wave is footward, to the left and posterior. The J and K loops are not significantly altered. Attention is called to the marked difference in amplitude of complexes in the H-F and A-P records.

If the records from Hamilton's "three directional ballistocardiograph" mentioned above be used to plot vector loops it will be seen that the axis of the I wave points about 30° to the left of the head-foot axis whereas in our subjects the I axis is almost invariably to the right of the head-foot axis.

The method described in this report has several obvious limitations and inadequacies, the most apparent of which is the lack of simultaniety of the records. This defect becomes all the more striking when one considers that successive ballistic complexes are not identical in form and size but vary considerably during the respiratory cycle. The variation in form is usually more striking in the lateral and A-P records than in the head-foot. Perusal of the records obtained in normal subjects suggests that the vector loops change in a rather consistent fashion during each respiratory cycle and are repetitive from one cycle to the next. In order to "fix" the vector loops in as standard a position as possible so that comparable complexes may be obtained in the three positions, respiration is suspended at approximately the same point in the cycle (mid-inspiration) while the records are being taken. That it is impossible to stop respiration at exactly the same

point each time hardly needs mention. However, the gross similarity of the loops in different normal subjects suggests that the errors involved are not overwhelming. It should be pointed out that the ballistocardiographic complex inscribed during suspended respiration need have no counterpart during ordinary respiration. It is not uncommon to see a record in which all ballistic complexes are grossly abnormal during ordinary respiration but in which the complexes become essentially normal when respiration is suspended. Consequently, the vector loops in some of the subjects with form abnormality appear more nearly normal solely as a result of suspended respiration.

It would be overly time-consuming and laborious if it were necessary to plot the vector loops in every case studied; fortunately, this is not necessary for a glance at the three records usually allows one to estimate grossly the magnitude and direction of the mean axes of the three major deflections (I, J and K). However, where phase differences exist in the three records, where there is gross form abnormality or where details of the loop are desired, it is necessary to plot the loops in the manner described above. When a method for simultaneous tri-directional recording becomes available it will then be possible to synthesize the loops electrically.

At the present juncture one is not justified in suggesting that the body motions delineated by the vector loops are related solely to cardiovascular phenomena; indeed, it is probable that they are not, for the ballistocardiographic bed not only accentuates or attenuates various frequency components in the record but probably also contributes actively to the formation of the ballistic complex. Furthermore, in a cross-coupled system such as the human body an impact along one axis may produce deflections in the other axes; therefore one cannot, at the present time, determine with any degree of precision what proportion of a deflection recorded along one axis actually arises from cardiovascular movements along that axis and what proportion is contributed by components originating in other axes. It is hoped that studies now in progress on the elastic properties and mechanical couplings of the body may shed light on this problem.

Until these studies and others relating to circulatory dynamics are carried out, it will be difficult to explain in physiological terms the

origin and significance of the vector loops. This fact does not deny the value of tri-directional recording as an empirical tool. It should be considered simply an extension of ordinary head-foot recording allowing more parameters for clinical correlation.

SUMMARY

1. The design of a simple ballistocardiographic turntable is described.

2. The use of this turntable permits ballistocardiographic records to be taken at any angle in the frontal plane of the body and in the anterior-posterior direction as well.

3. The recording of ballistocardiographic curves in the head-foot, lateral and anterior-posterior directions provides the data for a rough vectorial representation of body movements resulting from forces generated within the cardiovascular system.

4. Ballistocardiographic records and derived vector loops in a normal individual and in subjects with cardiovascular disease are shown.

5. It is suggested that further study of ballistocardiographic vectors may be profitable.

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BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of the Bulletin)

Lipidoses. Diseases of the Cellular Lipid Metabolism. By SIEGFRIED J. THANNHAUSER. Edited by HENRY A. CHRISTIAN. Reprinted from Oxford Loose-Leaf Medicine. 605 pp. $12.00. *Oxford University Press, New York.*

This revised edition of Dr. Thannhauser's monograph is an extraordinarily detailed and comprehensive review of current knowledge concerning diseases of lipid metabolism. He divides the xanthomatoses into three general groups. The first group is associated primarily with hypercholesterolemia and includes familial hypercholesterolemia, xanthomatous biliary cirrhosis, and the hypercholesterolemia of hypothyroidism. Dr. Thannhauser's opinions on the hereditary aspects of the xanthomatoses are not stated clearly enough. He now considers that biliary cirrhosis is primarily a disease of the liver rather than the result of obstruction of the common duct by xanthomatous atheromata. This view is more compatible with the extreme chronicity of icterus, which may be present for years before the appearance of obvious xanthomata. Moreover, xanthomatous biliary cirrhosis has now been described in the absence of xanthoma formation in the biliary duct. Treatment for familial xanthomatosis and xanthomatous biliary cirrhosis, says Dr. Thannhauser, should include a diet low in animal cholesterol. Vegetable sterols are not absorbed, and may be eaten with impunity.

The second group of xanthomatoses are those associated with an accumulation of neutral fats in the serum. Idiopathic hyperlipemia is associated with enlargement of the liver and spleen, and can be confused with xanthomatous biliary cirrhosis. However, in the latter disease jaundice is present and the serum is rich in cholesterol and phospholipids rather than in neutral fats. Hyperlipemia associated with cutaneous xanthomatoses also occurs in severe diabetes mellitus, in chronic pancreatitis, and in glycogen storage disease. Xanthomatoses have not been reported in association with the hyperlipemia of the nephrotic syndrome.

In the third group of xanthomatoses, Thannhauser includes those in which the serum lipids are normal, Schüller-Christian syndrome and eosinophilic granuloma of bone. The latter disease is now believed to be a localized form of Schüller-Christian syndrome. Thannhauser suggests that the accumulation of lipids in xanthoma cells in this syndrome is due to a "cellular disorder which manifests itself in an increased formation of cholesterol within the cell and the consecutive storage of this newly formed substance within the cell."

Gaucher's disease, Thannhauser postulates, is due to a "hypothetical imbalance of the enzymatic action concerned with cerebroside and sphingomyelin formation." The balance of enzymes which leads to cerebroside formation or disintegration is disturbed so that cerebrosides accumulate in the organs involved. A similar enzymic

imbalance, he thinks, is responsible for the accumulation of sphingomyelin in Niemann-Pick's disease.

Dr. Thannhauser's encyclopedic treatment of the lipidoses is an invaluable contribution to our understanding of current status of this most complex problem. It would be helpful if each of the discussions were concluded by a concise summary. The format of the book, in common with others of the same series, is excellent.

O. D. R.

Current Therapy. Edited by HOWARD F. CONN. 736 pp. $10.00. *W. B. Saunders Co. Philadelphia, Pa.*

Like the initial volume of this work in 1949, this revised edition attempts to bring "to the practicing physician authoritative information on the latest approved methods for treatment of disease." The value of this attempt of course depends on the authorities who are contributors. The editor has made very good selection of the two hundred fifty-odd contributors, however, all of them holding important teaching positions. He has attempted to have two or more contributions where different plans of treatment are equally acceptable. The articles are brief, but the range of subjects covered is remarkably wide. The regimens of treatment are based on sound rationale and usually on wide experience, and are uniformly of good quality. Where it is of importance, the complications of treatment and follow-up treatment are discussed. Remarks about experimental treatments and those of little value are often included.

Only three points seem deserving of criticism: there are no references cited, the volume is unnecessarily large, and the front cover places the publisher's name in undue prominence. However, the printing is excellent and the price reasonable.

This book is a valuable summary of currently acceptable therapeutic regimens, and should be especially helpful to the practitioner who does not have enough time to keep close contact with current literature.

R. E. M.

Annual Review of Medicine, vol. 1. Edited by W. C. CUTTING and H. W. NEWMAN assisted by A. BLALOCK, J. S. L. BROWNE, A. M. BUTLER, E. M. MACKAY and S. C. MADDEN. 484 pp. $6.00. *Annual Reviews, Inc. Stanford, California.*

A review of an annual review of such diversified subjects as allergy, otolaryngology, psychiatry, cardiac surgery, obstetrics and hematology cannot be particularly informative or critical. Suffice it to say that this is the first volume in a series made famous by the Annual Reviews of Biochemistry and the Annual Reviews of Physiology.

This first volume contains a number of really constructive and informative summaries of progress in recent years in such particular specialties as mentioned above. These reviews will continue to be helpful and stimulating, if it is possible to maintain the high standards of constructive analysis each year.

F. B. B.

Microphthalmos and Anophthalmos with or without Coincident Oligophrenia. By TORSTEN SJOGREN and TAGE LARSSON. 103 pp. 15 Swedish Kroner. *Ejnar Munksgaard, Copenhagen.*

Anomalies of the eye offer the geneticist an unusually happy hunting ground since they are obvious, even to the laity, commonly readily describable, and often bring their victims to public record in charitable institutions for the blind. The authors have taken advantage of these facts, as well as of the excellent and long-established Swedish school systems for the blind or mentally defective, to analyze 137 cases of microphthalmos of varying degree. Fifty-eight of these combined ocular defects, commonly micro- or anophthalmos, and defective visions of varying degrees, with mental deficiency of extreme grade in all cases but one, with epilepsy in one-third, and with skeletal abnormalities, usually kyphoscoleiosis, in two-thirds of the cases. The pedigrees are carefully worked out, and the authors feel that the condition is inherited as a partially sex-linked recessive characteristic. Toxoplasmosis and intrauterine rubella are adequately excluded as etiologic agents. The condition seems to merit a place among the other recognized, if not understood, hereditary malformations.

By contrast, seventy-nine cases of microphthalmos and visual impairment unassociated with mental defect were likewise unassociated with other described functional or organic disorders, and seemed to occur as a dominant hereditary disease with what the authors describe as "a low degree of manifestation."

The paper is carefully written and the material appears as satisfactory in respect to detail and accuracy of investigation as one could wish. It is to be hoped that some pathological investigations of these entities will soon appear.

D. B. C.

Child Hygiene in Baltimore and in Maryland. By J. H. MASON KNOX, Consultant, *Bureau of Child Hygiene, Maryland State Department of Health*, 1948. (36 p., unill.)

This very brief pamphlet records in a fashion so terse and clear that he who runs may read the development of the Child Hygiene Program in Maryland from its beginning around 1910 up until the present time. The article is written by a man who has been active in this field throughout his professional career and his solid basis of experience is shown throughout the article. One of the most unusual features about the pamphlet is the history of the private organizations which contributed to the reduction of infant mortality in this area. As has been pointed out so frequently, voluntary health organizations tend to become vested interests and self-perpetuating and remain to clutter up the scene after their services are no longer required. This has emphatically not been the case in connection with the Babies' Milk Fund and the Thomas Wilson Foundation, both of which, when they had completed the necessary demonstration bowed themselves out of existence, content that posterity would remember them for their contributions rather than that posterity should still see their names as active organizations.

The pamphlet is highly recommended as a quick glimpse of one phase, a very important phase, of the development of public health in Maryland.

P. V. L.

Epidemics in Schools. An Analysis of the Data Collected During the Years 1935 to 1939. By E. A. CHEESEMAN. Medical Research Council Special Report Series no. 271. 96 pp. 3s. net. *His Majesty's Stationery Office, London.*

This report is a sequel to a somewhat more extensive study, previously published, on the occurrence of epidemic diseases in English residential shcools during the period 1930–1934. The present report, covering the years 1935–1939, deals with a smaller number of schools, and lacks data by age groups of pupils. It consists chiefly of a presentation of incidence rates for conditions involving one or more days' absence from school, from two naval boarding schools, eleven boys' schools and five girls' schools, having a combined population of about 8,000 students. Only pupils in residence at the schools are included in the study. The principal disease groups studied are nasopharyngeal infections (which were the most frequent), influenza, the acute contagious diseases of childhood, rheumatism, otitis media, sinusitis, pneumonia and gastrointestinal disorders.

Attack rates for the three types of schools are computed on a term basis for the three terms of each year (no statement could be found as to the calendar period of a term; this information should have been given for the benefit of non-British readers). The terms are stated as Lent, Summer and Winter.

The author regards the sex difference in incidence of certain diseases as one of the major points of the study. He found the attack rate from nasopharyngeal infection in all terms of each year to be consistently higher in the girls' schools (as a group) than in the boys' schools.

This finding is considered in connection with evidence that measles spread more readily in boys' schools, and the absence in girls' schools of the statistical association between nasopharyngeal infections and otitis media or sinusitis which was shown for the boys' schools. The hypothesis is advanced that "in girls' schools the increased care taken to remove the mild cases of illness from the classroom has reduced both the incidence of more serious complications and the risk of wide dissemination of infectious disease."

Limited information is also provided on the occurrence of tuberculosis, jaundice, tinea cruris, conjunctivitis, appendicitis, and injuries. There is a brief section on time lost from school from all causes combined. The report provides confirmation of a number of observations made in the earlier period, and is at variance with certain others. It should be of interest to school health workers and epidemiologists.

P. E. S.

Psychosomatic Medicine, 2nd edition. By EDWARD WEISS and O. SPURGEON ENGLISH. 803 pp. $9.50. *W. B. Saunders Co., Philadelphia, Pa.*

The publication of the first edition of *Psychosomatic Medicine* seven years ago was a formidable task. Writing a first text on any subject is difficult, but

here the field is not enclosed by any specific boundaries and can readily be expanded to involve the entire subject of medical practice. The authors have done an excellent job in the revision for the second edition. Most major contributions to the field since the first edition have been included; a number of weaknesses have been overcome; and in general the new edition is far more useful than its predecessor. However, the general structure of the book, which has been retained, has shortcomings.

Psychosomatic medicine can be defined in a number of ways. The authors have, for practical reasons, chosen the broadest perspective and are actually presenting a book which will aid any physician or surgeon in acquiring an orientation towards psychiatric problems in his practice. The volume is not directed towards psychiatrists nor towards those persons who specifically interest themselves in that sphere of psychosomatic medicine which deals with emotional factors in medical illnesses. The volume concerns the influence of emotions upon illness of all types, including the physical or physiologic expression of the neuroses, and, the concerns of emotionally disturbed patients over their illnesses. This approach requires a very extensive text including a summary presentation of problems of personality development, psychiatric diagnosis, and psychiatric treatment. As might be anticipated in a work with such scope, the performance is spotty. There are excellent chapters and some that are quite superficial. The effort to cover the entire field of psychiatry in the first part of the book is unfortunately necessary for its purpose, and, though not always carried out too happily, the reviewer must admit that he would be hard pressed to name more than a few texts which would present an orientation to the problems of psychiatry that would be more useful. As with almost all psychiatric textbooks one can point out a number of shortcomings. One crucial sentence requires comment. They state, "If symptoms exist without a physical basis, or a physical disease fails to explain the symptoms completely, look for their meaning from the standpoint of behavior." This is sensible advice in general, but as the field of psychosomatic medicine proper is concerned with the emotional factors in diseases of a physical nature, this statement might readily lead to misunderstanding of the entire field. The psychopathology of psychosomatic diseases in general is presented in rather trite and oversimplified form. The authors wish to keep things at a level at which the general practitioner might be able to work, but it does not do justice to the profound nature of the emotional problems masked by the most common of the serious psychosomatic ailments, such as hypertension, ulcerative colitis, and asthma.

The second part of the volume is devoted to the application of psychiatric perspectives to the diseases of the various organ systems. A very sizable proportion of the material is concerned with symptomatology of various neuroses which are apt to be incorrectly diagnosed as organic diseases, such as the cardiac neuroses and various functional gastrointestinal disturbances. This, of course, is very useful to the practitioner but greatly dilutes the contents. A major weakness of the entire volume is the method of case presentation. The cases are usually very lengthy and not particularly well-pointed. Some such lengthy presentations are

useful, but the reviewer believes that the volume would gain by having more succinct case presentations with material that might be pertinent to the condition under discussion more sharply pointed up.

One might wish to debate certain views expressed, but the work as a whole has been very successfully carried out and constitutes a book that can be recommended to most physicians who wish an introduction to the field; and, the second part of the book forms a very handy reference for any worker in the field of psychosomatic medicine.

T. L.

Woman's Surgeon. The Life Story of J. Marion Sims. By SEALE HARRIS. 432 pp. $5.00. *The Macmillan Company, New York.*

This is the life story of J. Marion Sims, the "Father of Modern Gynecology," who in his time was called by some "the king" or "the prima donna." The autobiography of Sims is one of the best known of 77 medical autobiographies, but it deals primarily with the first fifty years of his life. "Woman's Surgeon" adds to these first fifty years and attempts to evaluate the stormy embitterment of the last two decades of his work.

There are few men in medicine who had a more colorful existence. Despite poor health, and with the assistance of his devoted slave patients, who were repeatedly operated upon without anesthesia in the pre-Listerian days, he devised the first successful method of repairing vesicovaginal fistulas. His contributions to gynecological surgery were legion and he was also in advance of his times in many phases of intra-abdominal surgery. He recommended cholecystostomy and one of his last pleas was for early surgical intervention in cases of gunshot wounds of the abdomen.

A "mercurial disposition" led to much misunderstanding, bitter resentments, and public accusations. Anxious to teach and to serve womankind, he became incensed when authorities limited the size of his gallery and denied him the right to admit cancer patients to the hospital. Under fire he resigned from the institution which he founded, Woman's Hospital in New York. Dirty linen was aired in public by Sims and his enemies, increasing the tempestuousness of his life.

He was not above self-praise, for in one address he declared that his silver wire sutures were the greatest medical advance of the century, not excluding anesthesia. A Southerner, living in the North, he solved the problem of the Civil War by going abroad where he captivated the medical profession and the courts. By the time of his death he forgave all his enemies except one. Sims, after death, continued to make medical history, for his autopsy report was the second reported case of coronary occlusion in the United States. The role of his wife, Theresa, throughout his earlier hardships and his later impatience and arguments is particularly well brought out in this book.

This book was a labor of love for Dr. Seale Harris, for in the South he had heard stories about Sims from early childhood. This is the accumulation of these stories and the additional recorded facts in the medical and lay publications. He

is to be commended for an interesting narrative. This book could not help but be well received by the non-medical, as well as the medical reader.

R. B. S.

Diseases of the Foot, 2nd edition. By EMIL D. W. HAUSER. 415 pp. $7.00. *W. B. Saunders Co. Philadelphia, Pa.*

This book is a complete treatise on the foot. It is well set up with fairly short chapters arranged very logically with a good bibliography placed conveniently at the end of each chapter. The book is not changed fundamentally from the first edition except to include the current antibiotics and use of cohesive bandage in the treatment of club feet.

The theme of the correction of pes valgo planus is repeated continuously through the book, and the functional gait with the shoe corrections which Dr. Hauser has popularized is likewise given repetitive mention. It is amply illustrated. The rare foot conditions are described in brief and accurate terms with appropriate bibliography to guide those interested in more details. The book is not one that is easily read as a continuous assignment, but any single problem about feet is presented quite interestingly and completely.

Dr. Hauser still makes use of the manipulative corrections of foot deformities using the Haglund foot board and Thomas wrenches with pictorial evidence of good results. The use of such strenuous manipulation is not without danger, and in many clinics has been given up in favor of operative techniques which are less traumatizing to the soft tissues. The use of these manipulative devices requires training and experience, and a beginner would do well to be careful with them.

This book is a valuable edition to the library of an orthopedic surgeon and even to the general practitioner whose practice is bound to include foot complaints and associated conditions.

E. J. McD.

Modern Surgical Technic. Second Edition. Four volumes and Index volume. By MAX THOREK. 3170 pages. $72.00. *J. B. Lippincott Company, Philadelphia, Pa.*

The first edition of *Modern Surgical Technic* was published in 1938 and subsequently went through eleven printings. Translations were made into Spanish and Portuguese. These are truly amazing facts since in the opinion of this reviewer the first edition constituted one of the more mediocre surgical treatises published in recent years. Dr. Thorek has now delivered himself of a four volume second edition of this work. The books are handsomely bound and beautifully printed on expensive paper. The text is profusely illustrated with black and white photographs and drawings as well as numerous color plates. However, the text, itself, leaves much to be desired.

The plan of presentation is an ambitious one. Part I of the first volume is devoted to "General Operative Considerations". Immediately one is confronted by such elegantly phrased profundities as, "The complete history taking of the patient . . . entails much care. Such important work never should be delegated to

nurses or other subordinates". A few pages later one reads that "Stomach lavage, enterostomy or suction drainage also will increase dehydration of the stomach". Phraseology and concepts of this type permeate the entire work.

After rather sketchy coverage of pre- and postoperative care and a concentrated and quite practical section on anesthesia, the reader is led through sections on blood transfusion, operating pavilions, sterilization and electrosurgery. Beginning with Part II one reaches the specific coverage of the general surgical management of lesions of the various anatomical regions. Here one encounters the real weaknesses and incongruities of *Modern Surgical Technic* There is a confusing use of eponyms in designating operative procedures throughout the text—for example, "John A. Jenny Modification of the Sano Method of Skin Grafting". All too frequently a well-recognized and adequate technic for conducting a given operative procedure is followed by one or more alternative methods of very questionable value. One of the many examples of this failing is seen in the section on Thyroid Surgery where the well-planned technical steps of subtotal thyroidectomy as detailed from articles by Hertzler and by Rienhoff are followed by a description of the totally inadequate "melon resection" of the thyroid as done by von Manteuffel in 1898. Nothing in the text suggests that the latter method is not perfectly satisfactory. Under the section on Parathyroids one finds consecutive subdivisions entitled "Parathyroidectomy for von Recklinghausen's Disease", "Parathyroidectomy for Hyperparathyroidism", "Parathyroidectomy for Tumor", and "Churchill and Cope Operation for Parathyroid Tumors Associated with Hyperparathyroidism". These bewildering subdivisions can only mean basic misunderstanding of the subject by the author.

In the number of pages devoted to specific subjects Dr. Thorek's personal interests and contributions are weighted strongly. For instance slightly more page space is devoted to plastic operations on the breasts (largely the author's procedures) than is allotted to surgical management of malignant and benign tumors of the breast. Similarly, under the section on Surgery of the Gallbladder, 22 pages are dedicated to the author's technique of "cholecystelectrocoagulectomy" or electro-surgical obliteration of the gallbladder.

In general the parts of the books devoted to the surgical specialities and subdivisions are lucid and concise presentations by a variety of Dr. Thorek's associates, each of whom has a special interest in the field which he discusses. These sections are for the most part devoid of the profusion of eponyms, lack of discrimination and out-moded technics that haunt the bulk of this work.

On the whole it must be said that a tremendous amount of information of a technical nature is contained in *Modern Surgical Technic*. The historical data, the bibliographies and the index are good sources of reference. The chief failing of the entire work is its lack of discrimination between the excellent technical procedure and the inferior and usually outmoded one. There is very little discussion of the rationale of the procedures described and practically no evaluation of results in application in terms of mortality, degree of accomplishment or limitation. These deficits accompanied by the many misspellings, the numerous examples of

tortured rhetoric, and other evidences of editorial laxity tend to make this second edition of *Modern Surgical Technic* an inadequate and confusing reference work, particularly for students and surgical house officers. In addition, the price ($72.00) is notably lacking in appeal.

H. W. S., Jr.

BOOKS RECEIVED FOR REVIEW

In Defense of Mothers. By LEO KANNER. 167 pp. $3.00. *Charles C Thomas, Springfield, Illinois.*

Epidemics in Schools. An Analysis of the Data Collected During the Years 1935 to 1939. By E. A. CHEESEMAN. Medical Research Council Special Report Series no. 271. 96 pp. 3s. net. *His Majesty's Stationery Office, London.*

Lippincott's *Quick Reference Book for Nurses*, 6th edition. Revised by Members of the Staff of the Columbia-Presbyterian Medical Center. 626 pp. $3.00. *J. B. Lippincott Co., Philadelphia, Pa.*

The Merck Manual of Diagnosis and Therapy. Thumb-Index Edition. 1592 pp. $5.00. *Merck & Co., Rahway, N. J.*

Morbus Caeruleus. Edited by E. MANNHEIMER. 332 pp. $9.25. *Interscience Publishers, New York.*

Pathology in General Surgery. By PAUL W. SCHAFER. 581 pp. $17.50. *The University of Chicago Press, Chicago, Illinois.*

The Physiology of Tissues and Organs. By DOUGLAS H. K. LEE. 159 pp. $4.00. *Charles C Thomas, Springfield, Illinois.*

Practice of Medicine, 5th edition. By JONATHAN CAMPBELL MEAKINS. 1558 pp. $13.50. *The C. V. Mosby Co., St. Louis, Missouri.*

Saints, Sinners and Psychiatry. By CAMILLA M. ANDERSON. 206 pp. $2.95. *J. B. Lippincott Co., Philadelphia, Pa.*